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		Results
1.	TITLE-ABSTR-KEY(matrix metalloproteinase 13) [All Sources(- All Sciences -)]	42

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*Atherosclerosis, In Press, Corrected Proof, Available online 28 December 2005,*  
Sophie Pégorier, Dominique Stengel, Hervé Durand, Martine Croset and Ewa Ninio  
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Atherosclerosis as a chronic inflammatory disease resulting from the imbalance of the pro- and anti-inflammatory factors in the vessel wall. PAF and PAF-like oxidized phospholipids generated upon LDL oxidation in the intima of the arteries may interact with infiltrated monocytes/macrophages and lead to the alteration of gene expression patterns accompanied by an impaired production of chemokines, interleukins and proteolytic and lipolytic enzymes. The aim of this study was to evaluate the binding capacity of the major component of PAF-like oxidized phospholipids, namely the 1-palmitoyl-2-oxovaleroyl-*sn*-glycero-3-phosphorylcholine (POVPC) to PAF-receptor (PAF-R) on the surface of human monocytes/macrophages and to further characterize the gene expression induced by such binding. We show that, POVPC binds to cultured human macrophages via PAF-R and transduces the signals leading to the intracellular Ca<sup>2+</sup> fluxes and modifies the transcription levels of numerous pro-inflammatory and pro-atherogenic genes. Although a some similarity of the gene expression patterns was observed when macrophages were activated with POVPC versus PAF, we observed that only POVPC treatment induced a several-fold activation of IL-8 gene. In turn, only PAF activated PAF-R, matrix metalloproteinase-13 and 15-lipoxygenase mRNA accumulation. Thus, we suggest, that POVPC signals in mature macrophages only in part through the PAF-R, a part of its effects may involve other receptors.

2. ☐ **Molecular pathways mediating mechanical signaling in bone • REVIEW ARTICLE**  

*Gene, In Press, Corrected Proof, Available online 19 December 2005,*  
Janet Rubin, Clinton Rubin and Christopher Rae Jacobs  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(482 K\)](#)

Bone tissue has the capacity to adapt to its functional environment such that its morphology is "optimized" for the mechanical demand. The adaptive nature of the skeleton poses an interesting set of biological questions (e.g., how does bone sense mechanical signals, what cells are the sensing system, what are the mechanical signals that drive the system, what receptors are responsible for transducing the mechanical signal, what are the molecular responses to the mechanical stimuli). Studies of the characteristics of the mechanical environment at the cellular level, the forces that bone cells recognize, and the integrated cellular responses are providing new information at an accelerating speed. This review first considers the mechanical factors that are generated by loading in the skeleton, including strain, stress and pressure. Mechanosensitive cells placed to recognize these forces in the

skeleton, osteoblasts, osteoclasts, osteocytes and cells of the vasculature are reviewed. The identity of the mechanoreceptor(s) is approached, with consideration of ion channels, integrins, connexins, the lipid membrane including caveolar and non-caveolar lipid rafts and the possibility that altering cell shape at the membrane or cytoskeleton alters integral signaling protein associations. The distal intracellular signaling systems on-line after the mechanoreceptor is activated are reviewed, including those emanating from G-proteins (e.g., intracellular calcium shifts), MAPKs, and nitric oxide. The ability to harness mechanical signals to improve bone health through devices and exercise is broached. Increased appreciation of the importance of the mechanical environment in regulating and determining the structural efficacy of the skeleton makes this an exciting time for further exploration of this area.

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3. ☐ **Potent, selective, and orally bioavailable matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis • ARTICLE**

*Bioorganic & Medicinal Chemistry, Volume 13, Issue 24, 15 December 2005, Pages 6629-6644*

Yonghan Hu, Jason S. Xiang, Martin J. DiGrandi, Xuemei Du, Manus Ipek, Leif M. Laakso, Jianchang Li, Wei Li, Thomas S. Rush, Jean Schmid *et al.*

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(335 K\)](#)

Modification of  $\alpha$ -biphenylsulfonamidocarboxylic acids led to potent and selective MMP-13 inhibitors. Compound 16 showed 100% oral bioavailability in rats and demonstrated >50% inhibition of bovine cartilage degradation at 10 ng/mL.

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4. ☐ **Differential expression of Janus kinase 3 (JAK3), matrix metalloproteinase 13 (MMP13), heat shock protein 60 (HSP60), and mouse double minute 2 (MDM2) in human colorectal cancer progression using human cancer cDNA microarrays • ARTICLE**

*Pathology - Research and Practice, Volume 201, Issue 12, 14 December 2005, Pages 777-789*

Daisuke Mori, Yuji Nakafusa, Kohji Miyazaki and Osamu Tokunaga

[Abstract](#)

In this study, we applied commercially available cDNA microarray systems (1068 genes) to investigate the genetic changes in six colorectal cancers (CRC). Thirty-two genes fell into the group of commonly upregulated genes. In addition, we immunohistochemically investigated the expression of the four top ranked upregulated genes, Janus kinase 3 (JAK3), matrix metalloproteinase 13 (MMP13), heat shock protein 60 (HSP60), and mouse double minute 2 (MDM2), in 44 CRC. JAK3 staining was located in the cancer cells. A comparison of JAK3 immunostaining and clinicopathological parameters showed a significant association of tumor differentiation, pT, and TMN stage. Staining of MMP13 and HSP60 was noted mainly in the cytoplasm of cancer cells. A significant association of these expressions was observed with tumor differentiation and pT. MDM2 staining was noted in the nucleus of cancer and non-cancer cells. No significant association of clinicopathological parameters with MDM2 expression was observed. In multivariate analysis, JAK3 immunoreactivity showed independent prognostically unfavorable predictors. These data suggest that JAK3, in particular, is a highly significant, prognostic immunohistochemical marker in CRC. This study proves that cDNA microarrays, plotted by a small number of genes from a few samples, are both practical and useful.

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5. ☐ **Locally applied angiogenic factors – a new therapeutic tool for meniscal repair • ARTICLE**

*Annals of Anatomy - Anatomischer Anzeiger, Volume 187, Issues 5-6, 2 November 2005, Pages 509-519*

Wolf Petersen, Thomas Pufe, Christian Stärke, Thomas Fuchs, Sebastian Kopf, Michael Raschke, Roland Becker and Bernhard Tillmann

[Abstract](#)

## Summary

Tears in the peripheral part of the menisci have a better healing potential than tears in the central part,

because the central two-thirds of the menisci are avascular. The avascular status of the meniscus is maintained by the expression of antiangiogenic factors such as endostatin. The distribution of endostatin in the menisci correlates with the degree of vascularization. Endostatin immunostaining is strong in the avascular zone and reduced in the vascularized outer one-third. Endostatin interacts with signal transduction of the vascular endothelial growth factor (VEGF) by reducing VEGF-induced kinase (Erk1/2) phosphorylation. VEGF plays an important role in angiogenesis in fetal menisci and it is down-regulated in the adult meniscus.

We hypothesized that healing of meniscal tears in the avascular zone can be promoted by the local application of the angiogenic factor VEGF. To evaluate this hypothesis a tear was created in the avascular zone of the medial meniscus in 18 merino sheep. The tear was then repaired with an uncoated suture (group 1), a suture coated with PDLLA (group 2), and by a suture coated with PDLLA/VEGF (group 3).

After 6 weeks we observed increased factor VIII immunostaining in the VEGF-treated group. However, in this treatment group (VEGF/PDLLA) no meniscus healed. In the uncoated suture group and in the PDLLA-coated suture group partial healing was observed in three animals and complete healing in three animals, respectively. Factor VIII expression is normally restricted to vascular endothelial cells. In this study, however, single endothelial cells could be detected in the menisci of the VEGF/PDLLA group. This finding suggests that the application of VEGF might have stimulated proliferation of vascular endothelial cells but the application of VEGF was not successful in stimulating the more complex process of vasculogenesis.

Further immunohistochemical examinations of the specimen have shown that in the VEGF/PDLLA group there is strong immunostaining against matrix metalloproteinase 13 (MMP-13). In vitro studies have shown that VEGF can stimulate chondrocytes to proliferate but also to express MMP-13 via HIF1- $\alpha$  induction. Since meniscal fibrochondrocytes express the VEGF receptor 2 (KDR) the induction of MMP expression might be another factor which inhibits healing despite increased angiogenesis.

In conclusion, the local application of VEGF via PDLLA-coated sutures does not promote meniscal healing. A single growth factor might not always be a promising tool for the promotion of tissue repair. Further studies have to find out if growth factor combinations (VEGF and angiopoietin) might be more effective in stimulating vasculogenesis during meniscal healing.

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6. ☐ **Integrin  $\alpha 1 \beta 1$  mediates collagen induction of MMP-13 expression in MC615 chondrocytes • ARTICLE**

*Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, Volume 1746, Issue 1, 30 October 2005, Pages 55-64*

Marie-Claire Ronzière, Elisabeth Aubert-Foucher, Jérôme Gouttenoire, Janine Bernaud, Daniel Herbage and Frédéric Mallein-Gerin

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During endochondral ossification, type I collagen is synthesized by osteoblasts together with some hypertrophic chondrocytes. Type I collagen has also been reported to be progressively synthesized in degenerative joints. Because Matrix Metalloproteinase-13 (MMP-13) plays an active role in remodeling cartilage in fetal development and osteoarthritic cartilage, we investigated whether type I collagen could activate MMP-13 expression in chondrocytes. We used a well-established chondrocytic cell line (MC615) and we found that MMP-13 expression was induced in MC615 cells cultured in type I collagen gel. We also found that  $\alpha 1 \beta 1$  integrin, a major collagen receptor, was expressed by MC615 cells and we further assessed the role of  $\alpha 1 \beta 1$  integrin in conducting MMP-13 expression. Induction of MMP-13 expression by collagen was potently and synergistically inhibited by blocking antibodies against  $\alpha 1$  and  $\beta 1$  integrin subunits, indicating that  $\alpha 1 \beta 1$  integrin mediates the MMP-13-inducing cellular signal generated by three-dimensional type I collagen. We also determined that activities of tyrosine kinase and ERK and JNK MAP kinases were required for this collagen-induced MMP-13 expression. Interestingly, bone morphogenetic protein (BMP)-2 opposed this induction, an effect that may be related to a role of BMP-2 in the maintenance of cartilage matrix.

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7. ☐ **Novel p38 mitogen-activated protein kinase inhibitor R-130823 protects cartilage by down-regulating matrix metalloproteinase-1,-13 and prostaglandin E<sub>2</sub> production in human chondrocytes • ARTICLE**

*International Immunopharmacology, In Press, Uncorrected Proof, Available online 24 August 2005,*  
Yoshihiro Wada, Kohei Shimada, Kotaro Sugimoto, Tomio Kimura and Shigeru Ushiyama  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(406 K\)](#)

In order to study the involvement of mitogen-activated protein kinase p38 in osteoarthritis, we investigated the effect of novel p38 inhibitor R-130823 {2-(4-fluorophenyl)-4-(1-phenethyl-1,2,3,6-tetrahydropyridin-4-yl)-3-(pyridin-4-yl)-1H-pyrrole} on human chondrocytes and bovine cartilage. In human primary chondrocytes, the production of matrix metalloproteinase-13 and -1 (MMP-13 and -1) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) was induced by interleukin-1 $\beta$ . Pretreatment with R-130823 inhibited the release of MMP-13, MMP-1 and PGE<sub>2</sub> with IC<sub>50</sub> values of 20, 230 and 3.9 nM, respectively. The inhibitory activity was also confirmed by a decrease in MMP-13 release from human chondrosarcoma cell line SW1353 with an IC<sub>50</sub> value of 17 nM. Ribonuclease protection assay on human primary chondrocytes indicated that MMP-13 and MMP-1 mRNA levels almost reached the maximum 14 h after IL-1 stimulation, while cyclooxygenase-2 (COX-2) mRNA quickly reached the maximum 4 h after the stimulation. R-130823 down-regulated the steady-state levels of MMP-13 and MMP-1 mRNA with IC<sub>50</sub> values of 4.2 and 79 nM, respectively. The COX-2 mRNA level was also suppressed with an IC<sub>50</sub> value of 21 nM. In the explant culture of bovine nasal cartilage, R-130823 suppressed the collagen cleavage induced by interleukin-1 $\alpha$  and oncostatin M, but not IL-1 $\beta$ -mediated glycosaminoglycan release. These results suggest that activated p38 accelerates cartilage breakdown by enhancing the expression of MMPs responsible for collagen cleavage, which thus implies chondroprotective effects of p38 inhibitors in osteoarthritis.

8. ☐ **Effect of genistein on the expression of bone metabolism genes in ovariectomized mice using a cDNA microarray • ARTICLE**

*The Journal of Nutritional Biochemistry, In Press, Corrected Proof, Available online 25 July 2005,*  
Jae-Eun Pie, Jin-Hee Park, Yoon-Hee Park, Yeon-Mi Ryu, Ki-Nam Kim, Seung-Woo Suh, Kevin G. Becker, Yoon S. Cho-Chung and Meyoung-kon Kim  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(246 K\)](#)

Osteoporosis associated with estrogen deficiency is defined as an abnormal decrease in bone mass leading to an increased fracture risk. Genistein (GEN), as a phytoestrogen, is a type of soybean-derived isoflavone that possesses structural similarity to estrogen. In this study, we assessed the effect of GEN in ovariectomized (OVX) mice. To determine the effect of GEN on bone metabolism, we investigated gene expression profiles using a radioactive cDNA microarray. Eight-week-old female mice were either sham operated (SHAM) or OVX. From 1 week after the operation, OVX mice were injected daily with intraperitoneal GEN (0.1, 0.5, 1.5 and 3.0 mg/day) or 17 $\beta$ -estradiol (E<sub>2</sub>, 0.03  $\mu$ g/day) for 4 weeks. A cDNA microarray was used to evaluate changes in the expression of 1,152 genes. OVX mice showed bone mineral density (BMD) loss versus SHAM mice (5.8 $\pm$ 0.4 vs. 6.9 $\pm$ 0.6 mg/cm<sup>2</sup>). However, femur BMDs were completely restored by GEN and by E<sub>2</sub> administration in OVX mice. Serum osteocalcin in OVX mice treated with 0.5 mg/day of GEN was 1.6-fold (44.30 $\pm$ 5.73 ng/ml) higher than that in untreated mice. GEN treatment up-regulated 38 genes (e.g., mitogen-activated protein kinase 10) and down-regulated 18 (e.g., matrix metalloproteinase 13). Moreover, GEN was found to have a protective effect on bone loss caused by estrogen deficiency in OVX mice. The present study suggests that GEN modulates bone metabolism-related gene expression, including calcitropic receptor, cytokines, growth factors and bone matrix proteins.

9. ☐ **Development of comprehensive functional genomic screens to identify novel mediators of osteoarthritis • ARTICLE**

*Osteoarthritis and Cartilage, Volume 13, Issue 6, June 2005, Pages 508-518*  
S. Daouti, B. Latario, S. Nagulapalli, F. Buxton, S. Uziel-Fusi, G.-W. Chirn, D. Bodian, C. Song, M.

## Summary

## Objective

The aim of this study was to develop high-throughput assays for the analysis of major chondrocyte functions that are important in osteoarthritis (OA) pathogenesis and methods for high-level gene expression and analysis in primary human chondrocytes.

## Methods

In the first approach, complementary DNA (cDNA) libraries were constructed from OA cartilage RNA and full-length clones were selected. These cDNAs were transferred into a retroviral vector using Gateway Technology. Full-length clones were over-expressed in human articular chondrocytes (HAC) by retroviral-mediated gene transfer. The induction of OA-associated markers, including aggrecanase-1 (Agg-1), matrix metalloproteinase-13 (MMP-13), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), collagen IIA and collagen X was measured by quantitative real-time polymerase chain reaction (QPCR). Induction of a marker gene was verified by independent isolation of 2–3 clones per gene, re-transfection followed by QPCR as well as nucleotide sequencing. In the second approach, whole cDNA libraries were transduced into chondrocytes and screened for chondrocyte cluster formation in three-dimensional agarose cultures.

## Results

Using green fluorescent protein (eGFP) as a marker gene, it was shown that the retroviral method has a transduction efficiency of >90%. A total of 40 verified hits were identified in the QPCR screen. The first set of 19 hits coordinately induced iNOS, COX-2, Agg-1 and MMP-13. The most potent of these genes were the tyrosine kinases Axl and Tyro-3, receptor interacting kinase-2 (RIPK2), tumor necrosis factor receptor 1A (TNFR1A), fibroblast growth factor (FGF) and its receptor FGFR, MUS81 endonuclease and Sentrin/SUMO-specific protease 3. The second set of seven hits induced both Agg-1 and MMP-13 but none of the other markers. Five of these seven genes regulate the phosphoinositide-3-kinase pathway. The most potently induced OA marker was iNOS. This marker was induced 20–500 fold by seven genes. Collagen IIA was also induced by seven genes, the most potent being transforming growth factor  $\beta$  (TGF $\beta$ )-stimulated protein TSC22, vascular endothelial growth factor (VEGF) and splicing factor 3a. This screening assay did not identify inducers of collagen X.

The second chondrocyte cluster formation screen identified 14 verified hits. Most of the genes inducing cluster formation were kinases. Additional genes had not been previously known to regulate chondrocyte cluster formation or any other chondrocyte function.

## Conclusions

The methods developed in this study can be applied to screen for genes capable of inducing an OA-like phenotype in chondrocytes on a genome-wide scale and identify novel mediators of OA pathogenesis. Thus, coordinated functional genomic approaches can be used to delineate key genes and pathways activated in complex human diseases such as OA.

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10. ☐ **FK506 suppresses the stimulation of matrix metalloproteinase 13 synthesis by interleukin-1 $\beta$  in rheumatoid synovial fibroblasts • ARTICLE**  
*Immunology Letters, Volume 98, Issue 2, 15 May 2005, Pages 194-199*  
Kiyoshi Migita, Taichiro Miyashita, Yumi Maeda, Takahiko Aoyagi, Yojiro Kawabe, Minoru Nakamura,

The aim of this study was to determine whether FK506, which has been shown to be effective for the treatment of refractory RA, affects the synthesis of matrix metalloproteinases (MMPs) in rheumatoid synovial fibroblasts. Synovial fibroblasts isolated from rheumatoid synovium were incubated in 6-well culture plates for 24 h with FK506 and interleukin-1 $\beta$ , alone and in combination. Samples of supernatants were assayed by ELISA or immunoblottings using anti-MMP-13 specific antibodies. In addition, synovial fibroblasts pretreated with FK506 were stimulated with IL-1 $\beta$  for 10 min and cellular lysates were subjected to anti-phospho-specific mitogen-activated protein kinase (MAPK). Unstimulated synovial fibroblasts produced low levels of MMP-3 and 13. IL-1 $\beta$ -induced substantial output of these MMPs into cell supernatants. FK506 had no detectable effects on IL-1 $\beta$ -induced MMP-2 induction. FK506, however, significantly suppressed MMP-13 production from IL-1 $\beta$ -stimulated synovial fibroblasts. FK506 also prevented IL-1 $\beta$ -stimulated JNK activation and transcriptional activation of AP-1 in these cells. Our results indicate that FK506 is capable of regulating MMP-13 synthesis via JNK pathway in rheumatoid synovium.

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11. ☐ **P90 Retroviral mediated RNA interference to knockdown matrix metalloproteinase 13 in human osteoarthritic chondrocytes • ABSTRACT**  
*Osteoarthritis and Cartilage, Volume 13, Supplement 1, 2005, Page S53*

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12. ☐ **Microarray analysis of proliferative and hypertrophic growth plate zones identifies differentiation markers and signal pathways • ARTICLE**  
*Bone, Volume 35, Issue 6, December 2004, Pages 1273-1293*  
Yan Wang, Frank Middleton, Jason A. Horton, Lee Reichel, Cornelia E. Farnum and Timothy A. Damron  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(1602 K\)](#)

Longitudinal bone growth results from coordination of proliferation and hypertrophy of chondrocytes, calcification of the matrix, vascular invasion, and completion of endochondral bone formation in the growth plate. Although proliferative and hypertrophic chondrocytes are well characterized histomorphologically, the understanding of factors governing this transition is not fully explained. Our hypothesis was that significant differential gene expression exists between proliferative and hypertrophic chondrocytes that may provide clues to the regulation of this transition at the transcriptional level. Normal Sprague-Dawley rat growth plate chondrocytes from the proliferative zone (PZ) and hypertrophic zone (HZ) were isolated by laser capture microdissection and then subjected to microarray analysis. Confirmation of the differential expression of selected genes was done by in situ hybridization and quantitative reverse transcription (RT) polymerase chain reaction (PCR). A total of 40 transcripts showed at least twofold greater expression in the PZ compared to HZ at both 6 and 7 weeks of age, while 52 transcripts showed twofold greater expression in the HZ compared to PZ at these time points. Many of the differentially expressed genes in each zone had very high levels of expression and thus were classified as "enriched transcripts" for that zone. The PZ-enriched transcripts included fibromodulin, proline arginine-rich end leucine-rich repeat protein, lactate dehydrogenase, and enolase 1 alpha. In contrast, HZ-enriched transcripts included collagen I, protein kinase (lysine deficient 4), proteasome (prosome, macropain) activator subunit 4, prostaglandin I2 synthase, and integrin-binding sialoprotein, **matrix metalloproteinase 13 (MMP13)**, and collagen X. Other genes were highly expressed in cells from both zones, including collagen II, aggrecan, cartilage oligomeric protein, cartilage link protein, laminin receptor, and eukaryotic translocation elongation factor. Functional classification of the PZ-enriched transcripts showed an increased percentage of genes expressed in nuclear cell cycle and transcription functions. In contrast, the HZ-enriched transcripts were more involved in extracellular structure and membrane receptor and transporter functions. Pathway analysis indicated that transforming growth factor  $\beta$  and parathyroid hormone-related protein (PTHrP) pathways were important in both zones, and bone morphogenic protein pathway played a role in the HZ. It is likely that these differentially expressed genes are involved in regulation of the transition from proliferation to differentiation functions in the growth plate.

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13. ☐ **Clinical pulmonary autograft valves: Pathologic evidence of adaptive remodeling in the aortic site • ARTICLE**  
*Journal of Thoracic and Cardiovascular Surgery, Volume 128, Issue 4, October 2004, Pages 552-561*  
Elena Rabkin-Aikawa, Masanori Aikawa, Mark Farber, Johannes R. Kratz, Guillermo Garcia-Cardena, Nicholas T. Kouchoukos, Max B. Mitchell, Richard A. Jonas and Frederick J. Schoen  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(705 K\)](#)

## Objective

We studied the pathologic features, cellular phenotypes, and matrix remodeling of clinical pulmonary-to-aortic valve transplants functioning up to 6 years.

## Methods

Nine autografts and associated vascular walls early (2-10 weeks) and late (3-6 years) postoperatively were examined by using routine morphologic methods and immunohistochemistry. In 4 cases autograft and homograft cusps were obtained from the same patients.

## Results

Autografts had near-normal trilaminar cuspal structure and collagen architecture and viable valvular interstitial and endothelial cells throughout the time course. In contrast, cusps of homografts used to replace the pulmonary valves in the same patients were devitalized. In early autograft explants,  $19.3\% \pm 2.4\%$  of cuspal interstitial cells were myofibroblasts expressing  $\alpha$ -actin. In contrast, myofibroblasts comprised only  $6.0\% \pm 1.1\%$  of cells in late explants and  $2.5\% \pm 0.4\%$  and  $4.6\% \pm 0.8\%$  of cells in normal pulmonary and aortic valves, respectively ( $P < .05$ ). In early autografts only  $12.0\% \pm 4.6\%$  of endothelial cells expressed the systemic arterial endothelial cell marker EphrinB2, whereas later explants had  $85.6\% \pm 5.4\%$  of endothelial cells expressing EphrinB2 ( $P < .05$ ). In early autografts  $43.8\% \pm 8.8\%$  of interstitial cells expressed metalloproteinase 13, whereas late autografts had  $11.4\% \pm 2.7\%$  of interstitial cells expressing matrix metalloproteinase 13 ( $P < .05$ ). Collagen content in autografts was comparable with that of normal valves and was higher than that seen in homograft valves ( $P < .005$ ). However, autograft walls were damaged, with granulation tissue (early) and scarring, with focal loss of normal smooth muscle cells, elastin, and collagen (late).

## Conclusions

The structure of pulmonary valves transplanted to the systemic circulation evolved toward that of normal aortic valves. Key processes in this remodeling included onset of a systemic endothelial cell phenotype and reversible plasticity of fibroblast-like valvular interstitial cells to myofibroblasts.

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14. ☐ **Inhibition of joint inflammation and destruction induced by anti-type II collagen antibody/lipopolysaccharide (LPS)-induced arthritis in mice due to deletion of macrophage migration inhibitory factor (MIF) • ARTICLE**  
*Cytokine, Volume 26, Issue 5, 7 June 2004, Pages 187-194*  
Hiroki Ichiyama, Shin Onodera, Jun Nishihira, Teruo Ishibashi, Toshinori Nakayama, Akio Minami, Kazunori Yasuda and Harukazu Tohyama  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(430 K\)](#)

## Objective

Previous studies have demonstrated that neutralization of macrophage migration inhibitory factor (MIF) by anti-MIF antibody decreases joint destruction in the collagen-induced arthritis model. The

present study was undertaken to investigate whether selective deletion of MIF inhibits inflammation and joint destruction of the anti-type II collagen antibody (anti-CII Ab)/lipopolysaccharide (LPS)-induced arthritis in mice, in order to determine the role of this cytokine in inflammatory arthritis.

## Design

Anti-CII Ab/LPS-induced arthritis was induced in MIF-deficient and wild-type mice. The effects of anti-MIF polyclonal antibody administration on anti-CII Ab-induced arthritis were also evaluated.

## Results

The expression of MIF protein and mRNA was induced in anti-CII Ab/LPS-induced arthritis joint tissues. Histopathological arthritis scores for synovial inflammation induced by anti-CII Ab/LPS - induced arthritis were significantly decreased in anti-MIF Ab-treated mice and in MIF-deficient mice compared to wild-type mice. In addition, mRNA levels of MMP-13 and MIP-2 in anti-CII Ab/LPS-induced arthritis joint tissues were significantly reduced in MIF-deficient mice compared to wild-type control mice.

## Conclusions

These results indicate that MIF plays a critical role in inflammation and joint destruction in the anti-CII Ab/LPS-induced arthritis model in mice, in part via induction of MMP-13 and neutrophil infiltration through the induction of MIP-2.

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15. ☐ **Tumor promoter-induced MMP-13 gene expression in a model of initiated epidermis • ARTICLE**  
*Biochemical and Biophysical Research Communications, Volume 317, Issue 2, 30 April 2004, Pages 570-577*  
Nicholette A. Zeliadt , Janel K. Warmka , Susanna E. Winston , Rachel Kahler , Jennifer J. Westendorf , Laura J. Mauro and Elizabeth V. Wattenberg  
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In mouse epidermis in vivo, the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) increases gene expression of matrix metalloproteinase-13 (MMP-13), an enzyme implicated in carcinogenesis. Here we used a keratinocyte cell line (308) derived from initiated mouse skin to investigate TPA-induced MMP-13 gene expression. Use of a pharmacological inhibitor (U0126) demonstrated that extracellular signal regulated kinase (ERK) plays a major role in TPA-induced MMP-13 gene expression. The 5'-flanking sequences of the MMP-13 gene contain binding sites for activator protein-1 (AP-1) and Runx. Both transcription factor families can be modulated by ERK and have been implicated in MMP-13 gene expression. TPA stimulated ERK-dependent increases in c-Fos protein and the c-Fos content of AP-1 complexes. MMP-13 promoter studies indicated that TPA requires AP-1, but not Runx, to induce MMP-13 gene expression. These studies show that in mouse keratinocytes MMP-13 gene expression can be induced through a Runx-independent pathway that involves the ERK-dependent modulation of AP-1.

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16. ☐ **Proteomic analysis of plasma proteins of workers exposed to benzene • ARTICLE**  
*Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Volume 558, Issues 1-2, 14 March 2004, Pages 35-44*  
Won-A Joo , Donggeun Sul , Do-Youn Lee , Eunil Lee and Chan-Wha Kim  
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In this study, we analyzed the proteins in plasma of workers exposed to benzene by two-dimensional gel electrophoresis, in the hope of finding a specific protein suitable for the biomonitoring of benzene exposure. Comet assays were also carried out to evaluate lymphocytes DNA damage. Fifty

workers from a printing company and 38 matched unexposed healthy subjects were enrolled in the study. DNA damage was found to be significantly higher in the exposed workers than in the controls. The tail moments of the two groups were  $2.07 \pm 0.35$  and  $1.48 \pm 0.41$ , respectively ( $P < 0.0001$ ). The mean values of *trans, trans*-muconic acid (*t,t*-MA) in workers exposed to benzene and in unexposed subjects were  $1.011 \pm 0.249$  and  $0.026 \pm 0.028$  mg/g creatinine, respectively. Protein profiles were significantly different ( $P < 0.05$ ) in the two groups, as identified by matrix-assisted laser desorption ionization/time of flight (MALDI-TOF) mass spectrometry and confirmed by Western blot. T cell receptor  $\beta$  chain (TCR  $\beta$ ), FK506-binding protein (FKBP51) and matrix metalloproteinase-13 (MMP13) were found to be up-regulated in the benzene-exposed workers. In addition, the correlation between TCR  $\beta$  and the tail moments of lymphocytes was statistically significant ( $r$ -value, 0.428). We conclude that TCR  $\beta$  in plasma could be used for the early detection of exposure to benzene.

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17. ☐ **Exogenous nucleosides modulate the expression of rat liver extracellular matrix genes in single cultures of primary hepatocytes and a liver stellate cell line and in their co-culture • ARTICLE**  
*Clinical Nutrition, Volume 23, Issue 1, February 2004, Pages 43-51*  
A. Arnaud, L. Fontana, M. J. Sáez-Lara, Á. Gil and J. M. López-Pedrosa  
Abstract

**Background & aims:** We have previously reported the antifibrotic effect of dietary nucleotides in cirrhotic rats. In this work, we used primary rat hepatocytes, a liver stellate cell line (CFSC-2G) and co-cultures of both cell types to investigate the effects of exogenous nucleosides on the gene expression of various extracellular matrix components and on markers of liver function, and to ascertain whether the effects found in vivo are due to CFSC-2G, hepatocytes, or are the consequence of cell-cell interactions.

**Results:** Nucleosides enhanced fibronectin, laminin, and  $\alpha 1(I)$  procollagen levels in CFSC-2G and hepatocytes, as well as collagen synthesis and secretion in CFSC-2G. In contrast, nucleosides lowered fibronectin, laminin and  $\alpha 1(I)$  procollagen levels, and decreased collagen synthesis in co-cultures. Matrix metalloproteinase-13 content and collagen secretion increased in co-cultures incubated with nucleosides. Albumin increased in hepatocytes and co-cultures incubated in the presence of nucleosides.

**Conclusions:** Nucleosides modulate the production of extracellular matrix in single cultures of hepatocytes and of CFSC-2G, and in co-cultures. This effect seems to be regulated at the translational level. The opposite behavior of single cultures and co-cultures is probably due to the fact that the latter model reproduces many of the physical and functional relationships observed in vivo between hepatocytes and stellate cells.

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18. ☐ **Immunolocalization of matrix metalloproteinase-13 on bone surface under osteoclasts in rat tibia • ARTICLE**  
*Bone, Volume 34, Issue 1, January 2004, Pages 48-56*  
Hiroaki Nakamura, Ginga Sato, Azumi Hirata and Toshio Yamamoto  
SummaryPlus | Full Text + Links | PDF (833 K)

Matrix metalloproteinase (MMP)-13 (an interstitial collagenase also called collagenase 3) is involved in degradation of extracellular matrix in various tissues. Using immunohistochemistry and Western blotting, we investigated localization of MMP-13 in rat tibia, to clarify the role of MMP-13 in bone resorption.

MMP-13 reactivity was mainly seen on bone surfaces under osteoclasts, and in some osteocytes and their lacunae near osteoclasts. However, immunoreactivity was not seen in chondrocytes or osteoclasts. MMP-13 was also localized on cement lines in the epiphysis. In the growth plate erosion zone, perivascular cells showed MMP-13 reactivity. Immunoelectron microscopy revealed that MMP-13 was localized on the bone surfaces, under the ruffled borders and some clear zones of osteoclasts. Gold-labeled MMP-13 was closely associated with collagen fibrils. Gold labeling was also detected in Golgi apparatus of osteocytes adjacent to osteoclasts and bone lining cells. Western

blotting showed that MMP-13 was mainly associated with mineralized bone matrix. These findings suggest that MMP-13 synthesized and secreted by osteoblast-lineage cells is localized under the ruffled borders of osteoclasts. MMP-13 may play an important role in degradation of type I collagen in bone matrix, acting in concert with cathepsin K and MMP-9 produced by osteoclasts. MMP-13 in perivascular cells may be involved in removal of cartilage matrix proteins such as type II collagen and aggrecan.

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19. ☐ **A novel cyclo-oxygenase-2 inhibitor modulates catabolic and antiinflammatory mediators in osteoarthritis • ARTICLE**  
*Biochemical Pharmacology, Volume 68, Issue 3, 1 August 2004, Pages 417-421*  
Patricia Fernández, Maria Isabel Guillén, Francisco Gomar, Enrique Aller, Pedro Molina and Maria José Alcaraz  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(258 K\)](#)

ITB (6-(*p*-bromophenyl)amino-7-(*p*-chlorophenyl)indazolo[2',3':1,5]-1,2,4-triazolo[4,3-*a*]-1,3,5-benzotriazepine) is a novel inhibitor of cyclo-oxygenase-2 (COX-2) with antiinflammatory activity in animal models. In the present study, we investigated the effect of this compound on the production of catabolic or antiinflammatory mediators in osteoarthritis (OA) cartilage. In OA cartilage explants, ITB inhibited the production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and matrix metalloproteinase-13 (MMP-13) in a concentration-dependent manner, whereas nitrite was partially reduced. On the contrary, ITB increased the production of interleukin (IL)-10 and the expression of heme oxygenase-1 (HO-1). ITB inhibited the production of catabolic mediators at concentrations able to increase IL-10 and HO-1 in OA cartilage, suggesting that this compound may be useful in the prevention of cartilage degradation.

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20. ☐ **Mitogen activated protein kinases selectively regulate palytoxin-stimulated gene expression in mouse keratinocytes • ARTICLE**  
*Toxicology and Applied Pharmacology, Volume 192, Issue 3, 1 November 2003, Pages 212-221*  
Nicholette A. Zeliadt, Janel K. Warmka and Elizabeth V. Wattenberg  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(277 K\)](#)

We have been investigating how the novel skin tumor promoter palytoxin transmits signals through mitogen activated protein kinases (MAPKs). Palytoxin activates three major MAPKs, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, in a keratinocyte cell line derived from initiated mouse skin (308). We previously showed that palytoxin requires ERK to increase matrix metalloproteinase-13 (MMP-13) gene expression, an enzyme implicated in carcinogenesis. Diverse stimuli require JNK and p38 to increase MMP-13 gene expression, however. We therefore used the JNK and p38 inhibitors SP 600125 and SB 202190, respectively, to investigate the role of these MAPKs in palytoxin-induced MMP-13 gene expression. Surprisingly, palytoxin does not require JNK and p38 to increase MMP-13 gene expression. Accordingly, ERK activation, independent of palytoxin and in the absence of JNK and p38 activation, is sufficient to induce MMP-13 gene expression in 308 keratinocytes. Dexamethasone, a synthetic glucocorticoid that inhibits activator protein-1 (AP-1), blocked palytoxin-stimulated MMP-13 gene expression. Therefore, the AP-1 site present in the promoter of the MMP-13 gene appears to be functional and to play a key role in palytoxin-stimulated gene expression. Previous studies showed that palytoxin simulates an ERK-dependent selective increase in the c-Fos content of AP-1 complexes that bind to the promoter of the MMP-13 gene. JNK and p38 can also modulate c-Fos. Palytoxin does not require JNK or p38 to increase c-Fos binding, however. Altogether, these studies indicate that ERK plays a distinctly essential role in transmitting palytoxin-stimulated signals to specific nuclear targets in keratinocytes derived from initiated mouse skin.

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21. ☐ **Induction of matrix metalloproteinase-13 gene expression by TNF- $\alpha$  is mediated by MAP kinases, AP-1, and NF- $\kappa$ B transcription factors in articular chondrocytes • ARTICLE**  
*Experimental Cell Research, Volume 288, Issue 1, 1 August 2003, Pages 208-217*

Abdelhamid Liacini, Judith Sylvester, Wen Qing Li, Wensheng Huang, Faramaze Dehnade, Mushtaq Ahmad and Muhammad Zafarullah  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(506 K\)](#)

Tumor necrosis factor alpha (TNF- $\alpha$ ), a major proinflammatory cytokine, induces arthritic joint inflammation and resorption of cartilage by matrix metalloproteinase-13 (MMP-13). RNA for MMP-13 is increased in human arthritic femoral cartilage. Mechanisms of this induction were investigated by pretreating primary human osteoarthritic (OA) femoral head chondrocytes or chondrosarcoma cells with the potential inhibitors of TNF- $\alpha$  signal transduction and downstream target transcription factors followed by stimulation with TNF- $\alpha$  and analysis of MMP-13 RNA/protein. TNF- $\alpha$  rapidly activated phosphorylation of extracellular signal-regulated kinases (ERKs), p38, and c-jun N-terminal kinase (JNK) mitogen-activated protein (MAP) kinases in human chondrocytes. Inhibitors of ERK (U0126, PD98059, and ERK1/2 antisense phosphorothioate oligonucleotide), JNK (SB203580, SP600125, and curcumin), and p38 (SB203580 and SB202190) pathways down-regulated the TNF-stimulated expression of MMP-13. Inhibitors of the transcription factors AP-1 (nordihydroguaiaretic acid, NDGA) and NF- $\kappa$ B (curcumin, proteasome inhibitors, and Bay-11-7085) suppressed TNF- $\alpha$ -induced MMP-13 expression in primary chondrocytes and SW1353 cells. These results suggest that induction of the MMP-13 gene by TNF- $\alpha$  is mediated by ERK, p38, and JNK MAP kinases as well as AP-1 and NF- $\kappa$ B transcription factors. Blockade of TNF- $\alpha$  signaling and its target transcription factors by the approaches tested here may be beneficial for reducing cartilage breakdown by MMP-13 in arthritis.

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22. ☐ **Vascular expression of matrix metalloproteinase-13 (collagenase-3) in basal cell carcinoma • ARTICLE**

*Experimental and Molecular Pathology, Volume 74, Issue 3, June 2003, Pages 230-237*

Yukari Hattori, Kamalakar C. Nerusu, Narasimharao Bhagavathula, Meghan Brennan, Noboru Hattori, Hedwig S. Murphy, Lyndon D. Su, Timothy S. Wang, Timothy M. Johnson and James Varani  
[Abstract](#)

Matrix metalloproteinase-13 (MMP-13; collagenase-3) was detected in the vasculature from 17 of 20 human basal cell carcinomas as assessed by immunohistology immediately after surgery. In contrast, MMP-1 (interstitial collagenase) was detected in the vasculature of only two of the same specimens. MMP-13 reactivity was also observed in the capillaries of normal human skin taken from the wound margin. Human dermal microvascular endothelial cells as well as human umbilical vein endothelial cells were isolated in culture and examined for MMP-13 expression. By reverse transcription-polymerase chain reaction and Southern blotting, an MMP-13 transcript was detected in unstimulated endothelial cells. The transcript was upregulated in cells treated with 50 nM phorbol myristate acetate (PMA). Western blotting demonstrated the presence of an anti-MMP-13 - immunoreactive protein in culture fluid from both cell sources. Immunoreactivity was stronger in culture fluid from cells treated with interleukin-1 $\alpha$  (IL-1 $\alpha$ ) than in culture fluid from control cells. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and PMA also upregulated MMP-13 expression but these agents were not as effective as IL-1 $\alpha$ . Additionally, reactivity was greater in culture fluid from endothelial cells grown on three-dimensional lattices of polymerized type I collagen than on dried collagen films. These data indicate that endothelial cells in the skin are a source of MMP-13 and that enzyme expression is upregulated under conditions that promote endothelial cell growth and vascular differentiation.

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23. ☐ **The expression of matrix metalloproteinase-13 and osteocalcin in mouse osteoblasts is related to osteoblastic differentiation and is modulated by 1,25-dihydroxyvitamin D3 and thyroid hormones • ARTICLE**

*Cell Biology International, Volume 27, Issue 6, June 2003, Pages 459-468*

Nadja Fratzl-Zelman, Helmut Glantschnig, Monika Rumpler, Alexander Nader, Adolf Ellinger and Franz Varga

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(1050 K\)](#)

Matrix metalloproteinase-13 (MMP-13), is a key protein of bone matrix degradation, and is highly expressed by osteoblasts. We used the osteoblast-like MC3T3-E1 cell line and compared the stimulatory effects of the bone resorptive agents 1,25-dihydroxyvitamin D<sub>3</sub> (1,25-(OH)<sub>2</sub>D<sub>3</sub>) 3,3',5-triido-L-thyronine (T3) on the expression of MMP-13 mRNA. We showed that the stimulatory effects were time and dose dependent, and were also transduced to the protein level, with 1,25-(OH)<sub>2</sub>D<sub>3</sub> being more potent.

MMP-13 expression in different mouse cells and its localization within developing bone from the onset of osteogenesis were also investigated. 1,25-(OH)<sub>2</sub>D<sub>3</sub>- and T3-regulated osteocalcin (Osc) expression in mouse osteoblasts was compared to hormonal effects on MMP-13 expression and activity. Here we show divergent and common roles of 1,25-(OH)<sub>2</sub>D<sub>3</sub> and T3 action on the expression of these marker proteins, depending on the stage of cell differentiation. In addition, we propose a role for MMP-13 in the bone collar of developing long bones. The results could help to more precisely characterize hormonal regulation in the developmental sequence of osteoblasts.

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24. ☐ **Extracellular Signal-Regulated Kinase Transmits Palytoxin-Stimulated Signals Leading to Altered Gene Expression in Mouse Keratinocytes • ARTICLE**

*Toxicology and Applied Pharmacology, Volume 185, Issue 1, 15 November 2002, Pages 8-17*

Janel K. Warmka, Susanna E. Winston, Nicholette A. Zeliadt and Elizabeth V. Wattenberg

[Abstract](#) | [Abstract + References](#) | [PDF \(191 K\)](#)

We have been probing the molecular mechanisms of tumor promoters that stimulate distinct initial signals to define critical downstream biochemical events in carcinogenesis. The action of the novel skin tumor promoter palytoxin on signaling and gene expression in keratinocytes, the primary target cells of tumor promoters, was therefore investigated. Palytoxin stimulated an increase in mRNA for matrix metalloproteinase-13 (MMP-13), an enzyme implicated in carcinogenesis, in a keratinocyte cell line derived from initiated mouse skin (308). Palytoxin stimulated an increase in c-Fos binding to the activator protein-1 (AP-1) site present in the promoter of the mouse MMP-13 gene. This effect was specific because palytoxin had little effect on c-Jun, JunB, JunD, FosB, Fra-1, or Fra-2 binding or on overall levels of transcription factor binding. The increase in c-Fos binding corresponded to a palytoxin-stimulated increase in c-Fos protein levels. Palytoxin stimulated the activation of the mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase, and p38. The MAPK kinase inhibitor PD 98059 blocked palytoxin-stimulated ERK activation. PD 98059 also blocked the palytoxin-stimulated increases in c-Fos protein levels, c-Fos binding to the AP-1 site, and MMP-13 mRNA. These studies identify important differences between palytoxin-stimulated signaling in keratinocytes derived from initiated mouse skin, the biologically relevant cell type, and other cell lines. Specifically, our data suggest that, in keratinocytes derived from initiated mouse skin, ERK plays an important role in transmitting palytoxin-stimulated signals to three downstream targets that are likely to affect carcinogenesis: c-Fos, AP-1, and MMP-13.

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25. ☐ **MMP13 promoter polymorphism is associated with atherosclerosis in the abdominal aorta of young black males • ARTICLE**

*Matrix Biology, Volume 21, Issue 6, October 2002, Pages 487-498*

Sungpil Yoon, Helena Kuivaniemi, Zoran Gatalica, Jane M. Olson, Giovanna Buttice, Siqin Ye, Brent A. Norris, Gray T. Malcom, Jack P. Strong and Gerard Tromp

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(1204 K\)](#)

Previous studies suggested that remodeling of connective tissue is important in progression of atherosclerosis. We investigated the importance of matrix metalloproteinase 13 (MMP13), in the pathogenesis of atherosclerosis using 995 samples from the Pathobiological Determinants of Atherosclerosis in Youth collection in an association study. We identified two new MMP13 promoter polymorphisms. The genotype for one of the MMP13 polymorphisms was associated with fibrous plaque ( $P=0.024$ ) in black males. Immunohistochemistry using antibodies for MMP13 showed that MMP13 is expressed in all layers of the aorta. In-vitro transfection experiments with reporter gene constructs and electrophoretic mobility-shift assays showed that the MMP13

polymorphism was a functional variant. MMP13 is therefore, a genetic risk factor for extent of fibrous plaque in the abdominal aorta in young black males. Elucidation of the currently unknown mechanism of the MMP13 polymorphism's action may provide for pharmacological intervention to reduce the severity of atherosclerotic changes in susceptible individuals.

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26. ☐ **Four Distinct Chondrocyte Populations in the Fetal Bovine Growth Plate: Highest Expression Levels of PTH/PTHrP Receptor, Indian Hedgehog, and MMP-13 in Hypertrophic Chondrocytes and Their Suppression by PTH (1–34) and PTHrP (1–40) • ARTICLE**  
*Experimental Cell Research, Volume 279, Issue 1, 10 September 2002, Pages 1-13*  
Jürgen Weisser, Silvia Riemer, Martina Schmidl, Larry J. Suva, Ernst Pöschl, Rolf Bräuer and Klaus von der Mark  
[Abstract](#) | [Abstract + References](#) | [PDF \(337 K\)](#)

Differentiation and growth of chondrocytes in fetal growth plates of vertebrate long bones and ribs appear to occur in a gradual, continuous manner between the resting zone through the proliferation zone, maturation zone, and upper and lower hypertrophic zones, with a continuous increase in cell size up to 10-fold of the volume of a resting chondrocyte. Here we provide evidence, however, that after centrifugation through a continuous Percoll gradient growth plate chondrocytes separate into four distinct cell populations (B1 to B4) which differ markedly in density, size, and gene expression. These populations collect in the absence of any phase borders in the gradient which might serve as concentration barriers. Fractions B1 and B2 contained the largest cells with the lowest buoyant density and showed the highest expression levels for type X collagen (Col X), but only the B1 population expressed high levels of matrix metalloproteinase-13 (collagenase 3). Cells in fraction B3 were significantly smaller and expressed little Col X, while cells in fraction B4 were of similar size to cells in the resting zone without significant Col X expression. The highest levels of parathyroid hormone (PTH)/PTH-related peptide (PTHrP) receptor (PTHR-1), and *Indian hedgehog* (*Ihh*) expression were also found in the hypertrophic fractions B1 and B2 and not in the prehypertrophic fraction B3, as expected from *in situ* hybridization data on PTHR-1 expression in fetal rodent or chicken growth plates. Incubation of fractions B1 to B3 with the amino-terminal fragments PTH (1–34) or PTHrP (1–40) suppressed the expression of Col X and PTHR-1 by more than 50% and the expression of *Ihh* nearly completely. In contrast, the mid-regional PTH fragment PTH (28–48) and PTH (52–84) consistently stimulated the expression of PTHR-1 by 10–20% in fractions B1 to B3. These findings confirm the existence of distinct differentiation stages within chondrocytes of the growth plate and support the hypothesis proposed by Vortkamp *et al.* (*Science* 273(1996)613) of a regulatory feedback loop of *Ihh* and PTH/PTHrP fragments controlling the differentiation of proliferating to prehypertrophic chondrocytes, but extend the ability to respond to PTH/PTHrP hypertrophic chondrocytes.

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27. ☐ **Dilinoleoylphosphatidylcholine prevents transforming growth factor- $\beta$ 1-mediated collagen accumulation in cultured rat hepatic stellate cells • ARTICLE**  
*Journal of Laboratory and Clinical Medicine, Volume 139, Issue 4, April 2002, Pages 202-210*  
Qi Cao, Ki M. Mak and Charles S. Lieber  
[Abstract](#)

Polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines, protects against alcoholic and nonalcoholic liver fibrosis in baboons and rats, respectively. In this study, we assessed the antifibrogenic action of dilinoleoylphosphatidylcholine (DLPC), the main phosphatidylcholine species of PPC, against transforming growth factor- $\beta$ 1-mediated expression of  $\alpha$ 1(I) procollagen, tissue inhibitor of metalloproteinase-1 (TIMP-1) and matrix metalloproteinase-13 (MMP-13) in cultured rat hepatic stellate cells (HSCs). In primary culture-activated HSCs, TGF- $\beta$ 1 up-regulated the  $\alpha$ 1(I) procollagen mRNA level with a concomitant increase in type I collagen accumulation in culture media. Whereas TIMP-1 mRNA levels and TIMP-1 accumulation in media were also increased by TGF- $\beta$ 1, MMP-13 mRNA expression and MMP-13 concentration in media were not altered. DLPC fully blocked TGF- $\beta$ 1-induced increase in  $\alpha$ 1(I) procollagen mRNA expression and decreased collagen accumulation in media. Whereas TIMP-1 mRNA level and TIMP-1 accumulation in media were decreased by DLPC, MMP-13 mRNA expression and MMP-13

concentration in media were not changed by this treatment. Palmitoyl-linoleoylphosphatidylcholine (PLPC), the second most abundant component of PPC, had no effect on the concentrations of collagen, TIMP-1, and MMP-13 in HSC culture. We conclude that DLPC prevents TGF- $\beta$ 1-mediated HSC fibrogenesis through down-regulation of  $\alpha$ 1(I) procollagen and TIMP-1 mRNA expression. The latter effect leads to a decreased accumulation of TIMP-1 that, in the presence of unchanged MMP-13 mRNA expression and MMP-13 concentration, results in a larger ratio of MMP-13/TIMP-1 concentrations in the culture media, favoring collagen degradation and lesser collagen accumulation. This effect of DLPC may explain, at least in part, the antifibrogenic action of PPC against alcoholic and other fibrotic disorders of the liver. (J Lab Clin Med 2002;139:202-10)

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28. ☐ **The cloning and functional analysis of canine matrix metalloproteinase-13 gene promoter • ARTICLE**

*Gene, Volume 286, Issue 2, 20 March 2002, Pages 233-240*

Sarah E. Campbell, Arvind Sood, David J. Argyle, Lubna Nasir, Sally Anne Argyle and David Bennett  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(427 K\)](#)

A fragment of the 5' untranslated region corresponding to the canine matrix metalloproteinase-13 (MMP-13), collagenase-3 gene promoter has been isolated and characterized in rat cardiocytes to investigate the role of MMP-13 in cardiac disease. The promoter fragment (1.5 kb) demonstrated regions of sequence homology with the collagenase gene promoter sequences already determined for other species. Conserved regions were identified and shown to correlate with DNA binding motifs including AP-1 sites, a nuclear factor (NF)  $\kappa$ B-like binding domain, GATA and Nkx2.5 sites. A consensus TATA box was identified and shown to direct transcription initiation approximately 27 bp upstream of the translation start site. The canine MMP-13 promoter fragment was sufficient to drive basal expression of a luciferase reporter gene in both Madin Darby canine kidney cells (MDCK) and primary rat cardiocytes. The activity of the promoter fragment could be significantly increased by the treatment of transfected primary rat cardiocytes with interleukin-1 (IL-1 $\beta$ ) and basic fibroblastic growth factor (bFGF), with some induction also observed with tumour necrosis factor (TNF $\alpha$ ). The canine MMP-13 promoter activity has also been compared to the basal and induced activity of the canine MMP-9, gelatinase B promoter in these cell types.

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29. ☐ **The Structure, Regulation, and Function of Human Matrix Metalloproteinase-13 • ARTICLE**  
*Critical Reviews in Biochemistry and Molecular Biology, Volume 37, Issue 3, 2002, Pages 149-166*  
Matthew F. Leeman, Stephanie Curran and Graeme I Murray  
[Abstract](#)

Matrix metalloproteinase-13 (MMP-13) is a proteolytic enzyme that belongs to a large family of extracellular matrix-degrading endopeptidases that are characterized by a zinc-binding motif at their catalytic sites. MMP-13 has a key role in the MMP activation cascade and appears to be critical in bone metabolism and homeostasis. It also has an important role in tumor invasion and metastasis. This commentary provides a detailed overview of the regulatory mechanisms, structure, and function of human MMP-13 and highlights the key factors involved in the biology of this important molecule.

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30. ☐ **Antifibrotic effect of silymarin in rat secondary biliary fibrosis is mediated by downregulation of procollagen  $\alpha$ 1(I) and TIMP-1 • ARTICLE**

*Journal of Hepatology, Volume 35, Issue 3, September 2001, Pages 392-398*

Ji-Dong Jia, Michael Bauer, Jae Jin Cho, Martin Ruehl, Stefano Milani, Gabriele Boigk, Ernst Otto Riecken and Detlef Schuppan  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(197 K\)](#)

**Background/Aims:** Silymarin reduces hepatic collagen accumulation by 35% in rats with secondary biliary cirrhosis. The aim of the present study was to explore its antifibrotic mechanism.

**Methods:** Thirty female adult Wistar rats were allocated to (1) bile duct occlusion, (2) bile duct

occlusion and oral silymarin at 50 mg/kg per day, and (3) sham operation and oral silymarin at 50 mg/kg per day. Steady-state mRNA levels for procollagen  $\alpha 1(I)$ , tissue inhibitor of metalloproteinases-1 (TIMP-1), and transforming growth factor (TGF)  $\beta 1$  were determined by multi-probe ribonuclease protection assay.

**Results:** After 6 weeks of bile duct occlusion, liver collagen content was increased 12-fold, when compared with the sham-operated controls. These animals displayed 17-, 6.5- and 16-fold higher transcript levels for procollagen  $\alpha 1(I)$ , TIMP-1 and TGF $\beta 1$  ( $P < 0.01$ ). Silymarin downregulated elevated procollagen  $\alpha 1(I)$ , TIMP-1 and TGF $\beta 1$  mRNA levels by 40–60% ( $P < 0.01$ ). These lowered hepatic profibrogenic transcript levels correlated with decreased serum levels of the aminoterminal propeptide of procollagen type III.

**Conclusions:** Silymarin suppresses expression of profibrogenic procollagen  $\alpha 1(I)$  and TIMP-1 most likely via downregulation of TGF $\beta 1$  mRNA in rats with biliary fibrosis. The serum procollagen type III propeptide level mirrors profibrogenic mRNA expression in the liver.

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31. ☐ **Design and synthesis of 2-oxo-imidazolidine-4-carboxylic acid hydroxyamides as potent matrix metalloproteinase-13 inhibitors • SHORT COMMUNICATION**

*Bioorganic & Medicinal Chemistry Letters, Volume 11, Issue 9, 7 May 2001, Pages 1211-1213*

Ralph P. Robinson, Ellen R. Laird, Kathleen M. Donahue, Lori L. Lopresti-Morrow, Peter G. Mitchell, Matthew R. Reese, Lisa M. Reeves, Amber I. Rouch, Ethan J. Stam and Sue A. Yocum

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(118 K\)](#)

A novel series of imidazolidinone-based matrix metalloproteinase (MMP) inhibitors was discovered by structural modification of pyrrolidinone 1a. Potent inhibition of MMP-13 was exhibited by the analogues having 4-(4-fluorophenoxy)phenyl (4a,  $IC_{50} = 3$  nM) and 4-(naphth-2-yloxy)phenyl (4h,  $IC_{50} = 4$  nM) as P1' groups.

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32. ☐ **Altered mRNA level of matrix metalloproteinase-13 in MH7A synovial cells under mechanical loading and unloading • ARTICLE**

*Bone, Volume 28, Issue 4, April 2001, Pages 399-403*

H. B. Sun and H. Yokota

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(208 K\)](#)

In an effort to elucidate the interplay between mechanical load and proteolytic gene expression in arthritic tissue degradation, we investigated cellular morphology and mRNA levels of matrix metalloproteinase-13 (MMP-13) genes under mechanical stress in human MH7A synovial cells. The cells were isolated from the knee joint of a rheumatoid arthritis patient. Using a reverse transcription-polymerase chain reaction procedure, we found that loading by an oscillatory shaker transiently decreased the level of MMP-13 mRNA and unloading by a clinostat increased its mRNA level. The unloaded cells appeared to be rounded and displayed a poorly developed track of peripheral fibers, whereas the cells under loading tended to align to the shear flow and were elongated. We also found that altering the oscillatory direction of mechanical loads contributed to a further reduction in mRNA expression of MMP-13. Our results demonstrate the role of mechanical loading and unloading in the transcriptional regulation of MMP-13 in synovial cells, and suggest the potential value of physical therapy for arthritic joints.

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33. ☐ **Cysteine proteinases in chondrosarcomas • ARTICLE**

*Matrix Biology, Volume 19, Issue 8, January 2001, Pages 717-725*

Mirva Söderström, Tauno Ekfors, Tom Böhling, Allan Aho, Hannu T. Aro and Eero Vuorio

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(1841 K\)](#)

The aim of the present study was to define the role of cathepsins B, H, K, L and S in the pathogenesis of human chondrosarcomas. For this purpose 40 tumour samples obtained from 12

patients with the diagnosis of conventional chondrosarcoma were systematically investigated for the expression of cathepsin mRNAs by Northern hybridisation, and for immunohistochemical localisation of the proteins. Northern analysis demonstrated the highest levels of cathepsins B and L in a recurring grade 1 chondrosarcoma, and in a grade 3 chondrosarcoma and in fibrous histiocytomas. Increased expression of cathepsin K mRNA was seen in seven chondrosarcomas, as well as in control tumours; fibrous histiocytomas, osteosarcomas, enchondromas and a giant cell tumour of bone. Cathepsin L was immunolocalised within the large chondrocytes, while cathepsin K was predominantly localised in large multinucleated osteoclastic cells and in some hypertrophic chondrocytes. These results suggest that chondrosarcoma can be included in the growing list of tumours, where cathepsins may well be involved in tumour progression. The simultaneous upregulation of cathepsins B and L, together with matrix metalloproteinase-13, and the association of cathepsin K with negative prognostic parameters suggests that an aggressive biological behaviour of chondrosarcoma may be related to the synthesis of cysteine proteinases and activation of other proteolytic enzymes. If this turns out to be the case, cathepsin inhibitors could provide the much needed adjuvant therapy for chondrosarcomas.

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34. ☐ **Monitor: molecules and profiles • SHORT SURVEY**

*Drug Discovery Today, Volume 5, Issue 10, 1 October 2000, Pages 477-480*

Andrew W. Lloyd

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(189 K\)](#)

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: Molecules summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; Profiles offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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35. ☐ **High-resolution solution structure of the catalytic fragment of human collagenase-3 (MMP-13) complexed with a hydroxamic acid inhibitor • ARTICLE**

*Journal of Molecular Biology, Volume 302, Issue 3, 22 September 2000, Pages 671-689*

Franklin J. Moy, Pranab K. Chanda, James M. Chen, Scott Cosmi, Wade Edris, Jeremy I. Levin and Robert Powers

[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(648 K\)](#)

The high-resolution solution structure of the catalytic fragment of human collagenase-3 (MMP-13) complexed with a sulfonamide derivative of a hydroxamic acid compound (WAY-151693) has been determined by multidimensional heteronuclear NMR. A total of 30 structures were calculated for residues 7–164 by means of hybrid distance geometry-simulated annealing using a total of 3280 experimental NMR restraints. The atomic rms distribution about the mean coordinate positions for the 30 structures is  $0.43(\pm 0.05)$  Å for the backbone atoms,  $0.80(\pm 0.09)$  Å for all atoms, and  $0.47(\pm 0.04)$  Å for all atoms excluding disordered side-chains. The overall structure of MMP-13 is composed of a  $\beta$ -sheet consisting of five  $\beta$ -strands in a mixed parallel and anti-parallel arrangement and three  $\alpha$ -helices where its overall fold is consistent with previously solved MMP structures. A comparison of the NMR structure of MMP-13 with the published 1.6 Å resolution X-ray structure indicates that the major differences between the structures is associated with loop dynamics and crystal-packing interactions. The side-chains of some active-site residues for the NMR and X-ray structures of MMP-13 adopt distinct conformations. This is attributed to the presence of unique inhibitors in the two structures that encounter distinct interactions with MMP-13. The major structural difference observed between the MMP-13 and MMP-1 NMR structures is the relative size and shape of the S1' pocket where this pocket is significantly longer for MMP-13, nearly reaching the surface of the protein. Additionally, MMP-1 and MMP-13 exhibit different dynamic properties for the active-site loop and the structural Zn-binding region. The inhibitor WAY-151693 is well defined in the MMP-13 active-site based on a total of 52 distance restraints. The binding motif of WAY-151693 in the MMP-13 complex is consistent with our previously reported MMP-1:CGS-27023A NMR structure and is similar to the MMP-13: RS-130830 X-ray structure.

36. ☐ **Matrix metalloproteinase-13 expression in rabbit knee joint connective tissues: influence of maturation and response to injury • ARTICLE**  
*Matrix Biology, Volume 19, Issue 5, September 2000, Pages 431-441*  
Marie-Pierre Hellio Le Graverand, Jonna Eggerer, Paul Sciore, Carol Reno, Eric Vignon, Ivan Otterness and David A. Hart  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(480 K\)](#)

The hypothesis of the present work was that expression of matrix metalloproteinase-13 (MMP-13, collagenase-3) would be induced during conditions involving important matrix remodeling such as ligament maturation, scar healing and joint instability. Therefore, MMP-13 expression in the medial collateral ligament (MCL) during the variable situations of tissue maturation and healing was assessed. MMP-13 expression in three intra-articular connective tissues of the knee (i.e. articular cartilage, menisci and synovium) following the transection of the anterior cruciate ligament of the knee was evaluated at 3 and 8 weeks post-injury. MMP-13 mRNA (semi-quantitative RT-PCR) and protein (immunohistochemistry and Western blotting) were detected in all of the tissues studied. Significantly higher MCL mRNA levels for MMP-13 were detected during the early phases of tissue maturation (i.e. 29 days in utero and 2-month-old rabbits) compared to later phases (5- and 12-month-old rabbits). This pattern of expression was recapitulated following MCL injury, with very high levels of expression in scar tissue at 3 weeks post-injury and then a decline to levels not significantly different from control values by 14 weeks. Elevated mRNA levels correlated with increased protein levels for MMP-13 in both menisci and synovium following the transection of the anterior cruciate ligament and during medial collateral ligament healing. These results indicate that MMP-13 expression is regulated by a number of variables and that high levels of expression occur in situations when connective tissue remodeling is very active.

37. ☐ **Solution structure of the catalytic domain of human collagenase-3 (MMP-13) complexed to a potent non-peptidic sulfonamide inhibitor: binding comparison with stromelysin-1 and collagenase-1 • ARTICLE**  
*Journal of Molecular Biology, Volume 301, Issue 2, 11 August 2000, Pages 513-524*  
Xiaolu Zhang, Nina C. Gonnella, James Koehn, Naveen Pathak, Vishwas Ganu, Richard Melton, David Parker, Shu-Ih Hu and Ki-Yean Nam  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(516 K\)](#)

The full three-dimensional structure of the catalytic domain of human collagenase-3 (MMP-13) complexed to a potent, sulfonamide hydroxamic acid inhibitor (CGS 27023) has been determined by NMR spectroscopy. The results reveal a core domain for the protein consisting of three  $\alpha$ -helices and five  $\beta$ -sheet strands with an overall tertiary fold similar to the catalytic domains of other matrix metalloproteinase family members. The S1' pocket, which is the major site of hydrophobic binding interaction, was found to be a wide cleft spanning the length of the protein and presenting facile opportunity for inhibitor extension deep into the pocket. Comparison with the reported X-ray structure of collagenase-3 showed evidence of flexibility for the loop region flanking the S1' pocket in both NMR and X-ray data. This flexibility was corroborated by NMR dynamics studies. Inhibitor binding placed the methoxy phenyl ring in the S1' pocket with the remainder of the molecule primarily solvent-exposed. The binding mode for this inhibitor was found to be similar with respect to stromelysin-1 and collagenase-1; however, subtle comparative differences in the interactions between inhibitor and enzyme were observed for the three MMPs that were consistent with their respective binding potencies.

38. ☐ **Enhanced Interstitial Collagenase (Matrix Metalloproteinase-13) Production of Kupffer Cell by Gadolinium Chloride Prevents Pig Serum-Induced Rat Liver Fibrosis • ARTICLE**  
*Biochemical and Biophysical Research Communications, Volume 267, Issue 1, 7 January 2000, Pages 290-295*  
Koji Hironaka, Isao Sakaida, Yasuhiro Matsumura, Seiji Kaino, Koji Miyamoto and Kiwamu Okita  
[Abstract](#) | [Abstract + References](#) | [PDF \(344 K\)](#)

Hepatic fibrosis results from an imbalance between fibrogenesis and fibrolysis in the liver. It remains uninvestigated whether Kupffer cells produce matrix metalloproteinase-13 (MMP-13), which mainly hydrolyzes extracellular matrix (ECM). We sought to determine the role of Kupffer cells in fibrogenesis/fibrolysis. *In vivo*, we used the rat model of pig serum-induced liver fibrosis. A subset was treated with gadolinium chloride (GdCl<sub>3</sub>), which specifically acts on Kupffer cells.

Administration of GdCl<sub>3</sub> remarkably decreased the hydroxyproline content of the liver and increased the expression of MMP-13 mRNA in the liver without a difference in procollagen type I and tissue inhibitors of metalloproteinase-1 (TIMP-1) mRNA expression on Northern blot analysis with the elimination of ED2-positive cells. *In vitro*, addition of GdCl<sub>3</sub> to isolated Kupffer cells showed increased type I collagen-degrading activity in a dose-dependent manner as well as MMP-13 mRNA expression on Northern blot analysis. It is concluded that Kupffer cells are a major source of MMP-13 and modulation of Kupffer cells by GdCl<sub>3</sub> prevents liver fibrosis with increased expression of MMP-13 mRNA and protein, whereas procollagen type I and TIMP-1 mRNA, which encode two major effectors of fibrogenesis, were unchanged. This is the first report showing that Kupffer cells produce interstitial collagenase (MMP-13) resulting in the reduction of ECM. This discovery may provide new insights into therapy for hepatic fibrosis.

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39. ☐ **Does adult fracture repair recapitulate embryonic skeletal formation? • ARTICLE**  
*Mechanisms of Development, Volume 87, Issues 1-2, 1 September 1999, Pages 57-66*  
Cristin Ferguson, Eytan Alpern, Theodore Miclau and Jill A. Helms  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(2151 K\)](#)

Bone formation is a continuous process that begins during fetal development and persists throughout life as a remodeling process. In the event of injury, bones heal by generating new bone rather than scar tissue; thus, it can accurately be described as a regenerative process. To elucidate the extent to which fetal skeletal development and skeletal regeneration are similar, we performed a series of detailed expression analyses using a number of genes that regulate key stages of endochondral ossification. They included genes in the *indian hedgehog* (*ihh*) and core binding factor 1 (*cbfal*) pathways, and genes associated with extracellular matrix remodeling and vascular invasion including vascular endothelial growth factor (*VEGF*) and matrix metalloproteinase 13 (*mmp13*). Our analyses suggested that even at the earliest stages of mesenchymal cell condensation, chondrocyte (*ihh*, *cbfal* and collagen type II-positive) and perichondrial (*gli1* and *osteocalcin*-positive) cell populations were already specified. As chondrocytes matured, they continued to express *cbfal* and *ihh* whereas *cbfal*, *osteocalcin* and *gli1* persisted in presumptive periosteal cells. Later, *VEGF* and *mmp13* transcripts were abundant in chondrocytes as they underwent hypertrophy and terminal differentiation. Based on these expression patterns and available genetic data, we propose a model where *Ihh* and *Cbfa1*, together with *Gli1* and *Osteocalcin* participate in establishing reciprocal signal site of injury. The persistence of *cbfal* and *ihh*, and their targets *osteocalcin* and *gli1*, in the callus suggests comparable processes of chondrocyte maturation and specification of a neo-perichondrium occur following injury. *VEGF* and *mmp13* are expressed during the later stages of healing, coincident with the onset of vascularization of the callus and subsequent ossification. Taken together, these data suggest the genetic mechanisms regulating fetal skeletogenesis also regulate adult skeletal regeneration, and point to important regulators of angiogenesis and ossification in bone regeneration.

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40. ☐ **Expression of metalloproteinase-13 (collagenase-3) is induced during fracture healing in mice • ARTICLE**  
*Bone, Volume 25, Issue 2, August 1999, Pages 197-203*  
H. Yamagiwa, K. Tokunaga, T. Hayami, H. Hatano, M. Uchida, N. Endo and H. E. Takahashi  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(806 K\)](#)

In fracture healing, a large amount of cartilage is formed, then rapidly replaced by osseous tissue. This process requires the transition of extracellular matrix component from type II to type I collagen. We investigated the expression of matrix metalloproteinase-13 (MMP-13), which has a high potential to cleave type II as well as type I collagen, during fracture repair in mouse ribs. *In situ* hybridization demonstrated that MMP-13 mRNA was present throughout the healing process. It was detected in the cells of the periosteum at day 1. As fracture callus grew, strong MMP-13 mRNA

signals were detected in cells of the cartilaginous callus. In the reparative and remodeling phases, both hypertrophic chondrocytes and immature osteoblastic cells in the fracture callus expressed MMP-13 mRNA strongly. These cells were located adjacent to tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts at the sites of cartilage/bone transition. In osteoclasts, MMP-13 expression was not detected. The level of MMP-13 mRNA peaked at day 14 postfracture by northern blotting. Immunohistochemical staining showed that MMP-13 was detected primarily in hypertrophic chondrocytes. These results indicate that MMP-13 is induced during fracture healing. The site- and cell-specific expression of MMP-13 and its enzymatic property suggest that MMP-13 initiates the degradation of cartilage matrix, resulting in resorption and remodeling of the callus. In conclusion, MMP-13 plays an important role in the healing process of fractured bone in mice.

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41. ☐ **Expression of matrix metalloproteinase-13 and tissue inhibitor of metalloproteinase-1 in acute liver injury • ARTICLE**

*Journal of Hepatology, Volume 30, Issue 3, March 1999, Pages 419-424*

Yutaka Yata, Terumi Takahara, Kei Furui, Li Ping Zhang and Akiharu Watanabe  
[SummaryPlus](#) | [Full Text + Links](#) | [PDF \(550 K\)](#)

**Background/Aims:** Matrix metalloproteinase-13, one of the principal neutral proteinases capable of cleaving native fibrillar collagens, is important in the degradation and remodeling of extracellular matrix. However, its precise expression in liver injury has not been characterized. We examined the kinetics of the expression of matrix metalloproteinase-13 and one of its specific inhibitors, tissue inhibitor of metalloproteinase-1, in acute liver injury in rats.

**Methods:** Acute liver injury was induced by administration of carbon tetrachloride or two different doses of D-galactosamine hydrochloride in Wistar rats. Hepatic matrix metalloproteinase-13 and tissue inhibitor of metalloproteinase-1 mRNA levels were then examined by Northern blotting.

**Results:** All rats survived after liver injury induced by carbon tetrachloride or low doses of D-galactosamine hydrochloride. However, rats died 5 days after induction of liver injury by high doses of D-galactosamine hydrochloride. In carbon tetrachloride-induced liver injury, matrix metalloproteinase-13 mRNA was transiently increased between 6 h and 1 day after injury. Tissue inhibitor of metalloproteinase-1 mRNA expression was increased between 6 h and 3 days after the peak of matrix metalloproteinase-13 expression. Similar patterns of matrix metalloproteinase-13 and tissue inhibitor of metalloproteinase-1 expression were observed in low-dose D-galactosamine hydrochloride-induced liver injury. In contrast, in high-dose D-galactosamine hydrochloride-induced liver injury, tissue inhibitor of metalloproteinase-1 expression peaked before matrix metalloproteinase-13 expression, which was increased 2 days after injury. Both mRNA levels continued to increase until death.

**Conclusions:** Transient expression of matrix metalloproteinase-13, followed by that of tissue inhibitor of metalloproteinase-1, was observed during recovery from acute liver injury induced by carbon tetrachloride and low-dose D-galactosamine hydrochloride. In contrast, disordered expression of matrix metalloproteinase-13 was observed in fatal liver injury caused by high-dose D-galactosamine hydrochloride. These results indicate that matrix metalloproteinase-13 plays an important role in the early phase of recovery from liver injury.

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42. ☐ ***Salvia miltiorrhiza* reduces experimentally-induced hepatic fibrosis in rats • ARTICLE**

*Journal of Hepatology, Volume 29, Issue 5, November 1998, Pages 760-771*

Shanthi Wasser, Jean May Sian Ho, Hui Kheng Ang and Carolyn Eng Looi Tan  
[Abstract](#) | [Abstract + References](#) | [PDF \(899 K\)](#)

**Background/Aims:** Hepatic fibrosis occurs as a result of injury to the liver parenchyma and biliary system. We have studied the effect of the traditional Chinese medicinal herb, *Salvia miltiorrhiza*, in an experimental model of hepatic fibrosis and evaluated its effect on various paradigms involved in hepatic fibrosis.

**Methods:** Liver fibrosis was induced in male Wistar rats by chronic administration of carbon tetrachloride for 10 weeks. The carbon tetrachloride-treated rats were randomly assigned to three groups: no treatment, *Salvia* for 12 weeks from the onset of carbon tetrachloride treatment, and *Salvia* for 2 weeks after the completion of the 10-week course. The normal control groups in the study were: neither carbon tetrachloride nor *Salvia*, and *Salvia* only for 12 weeks. The livers were graded histologically and analyzed by reverse transcription-polymerase chain reaction for the transcription of genes involved in liver fibrosis, namely, transforming growth factor- $\beta$ 1 and the extracellular matrix components procollagens I and III, tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-13. The transcripts were normalized against that of glyceraldehyde-3-phosphate dehydrogenase and analyzed statistically.

**Results:** The histological evaluation showed that *Salvia* could reverse the fibrosis caused by carbon tetrachloride treatment. Rats treated with the herb had reduced levels of transforming growth factor- $\beta$ 1, procollagens I and III and tissue inhibitor of metalloproteinase-1 transcripts and an increased level of matrix metalloproteinase-13 transcript, when compared to the disease control.

**Conclusions:** *Salvia miltiorrhiza*, a cheap and widely available herb, significantly reduces carbon tetrachloride-induced hepatic fibrosis in rats.

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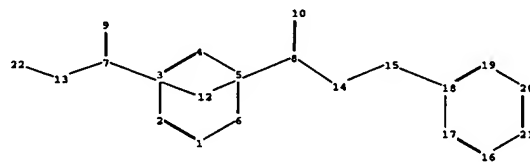
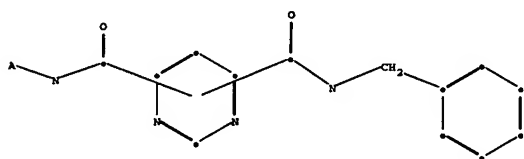
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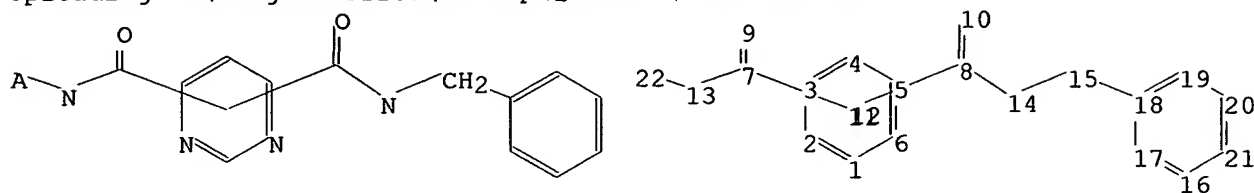
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exact/norm bonds :

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exact bonds :

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normalized bonds :

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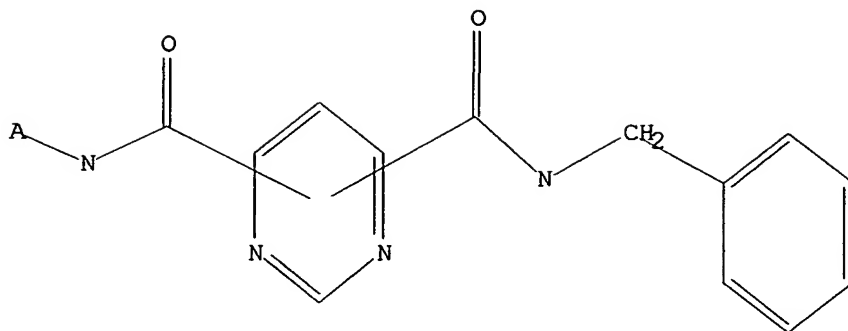
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L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2005:174538 CAPLUS

DN 142:423035

TI Structural Basis for the Highly Selective Inhibition of MMP-13

AU Engel, Christian K.; Pirard, Bernard; Schimanski, Sandra; Kirsch, Reinhard; Habermann, Joerg; Klingler, Otmar; Schlotte, Volkhard; Weithmann, Klaus Ulrich; Wendt, K. Ulrich

CS A Company of the Sanofi-Aventis Group, Industrial Park Hoechst, Aventis Pharma Deutschland GmbH, Frankfurt, D-65926, Germany

SO Chemistry & Biology (2005), 12(2), 181-189

CODEN: CBOLE2; ISSN: 1074-5521

PB Cell Press

DT Journal

LA English

AB Summary: Inhibitors for matrix metalloproteinases (MMPs) are under investigation for the treatment of cancer, arthritis, and cardiovascular disease. Here, the authors report a class of highly selective MMP-13 inhibitors (pyrimidine dicarboxamides) that exhibit no detectable activity against other MMPs. The high-resolution x-ray structures of three mols. of this series bound to MMP-13 reveal a novel binding mode characterized by the absence of interactions between the inhibitors and the catalytic zinc. The inhibitors bind in the S1' pocket and extend into an addnl. S1' side pocket, which is unique to MMP-13. The authors analyze the determinants for selectivity and describe the rational design of improved compds. with low nanomolar affinity.

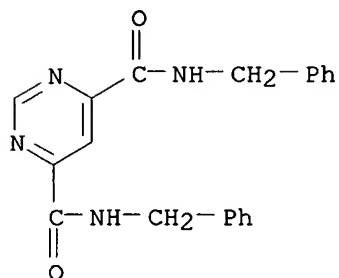
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(structural basis for highly selective inhibition of MMP-13)

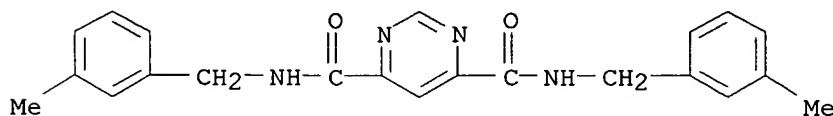
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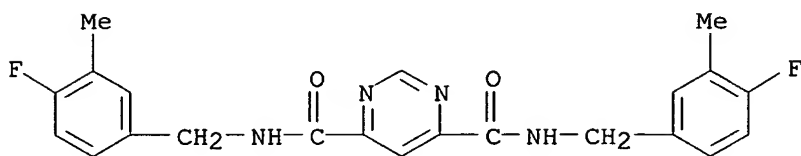


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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:564126 CAPLUS  
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 TI Preparation of pyrimidinedicarboxamides as selective MMP 13 inhibitors  
 IN Klingler, Otmar; Kirsch, Reinhard; Habermann, Joerg; Weithmann,  
 Klaus-Ulrich; Engel, Christian; Pirard, Bernard  
 PA Aventis Pharma Deutschland G.m.b.H., Germany  
 SO Ger. Offen., 35 pp.  
 CODEN: GWXXBX

DT Patent

LA German

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OS MARPAT 141:106493

AB Title compds. I [R1 = H, alkyl; R2 = (un)substituted alkyl; R3-R7 = H, halogen, (un)substituted alkyl, alkoxy, alkylthio] were prepared for use as selective inhibitors of collagenase (MMP13). Thus, 4-HOC6H4CHO was treated with BrCH2CO2CMe3 to give 4-OCHC6H4CH2CO2CMe3 which was converted to its oxime and reduced to the amine. This amine was used to acylate the pyrimidinecarboxylic acid fragment to give I [NR1R2 = OCMe3, R3-R5 = H, R6 = F, R7 = Me] which has IC50 for inhibition of MMP13 of 12 nM.

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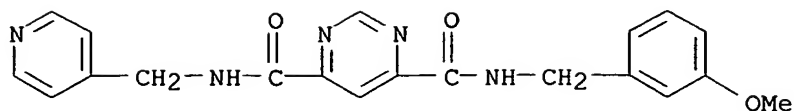
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(preparation of pyrimidinedicarboxamides as selective MMP 13 inhibitors)

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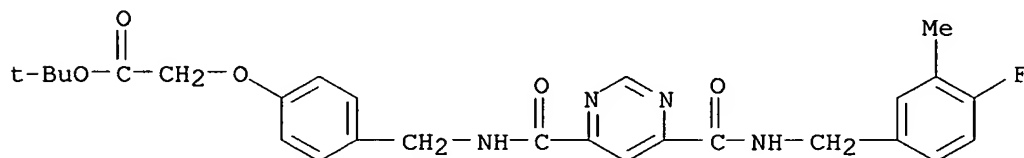
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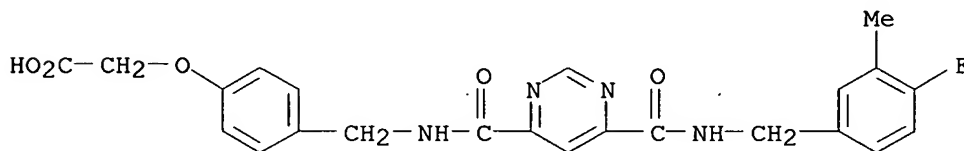
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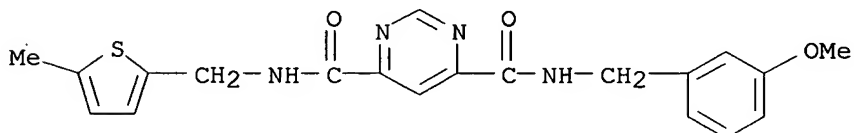
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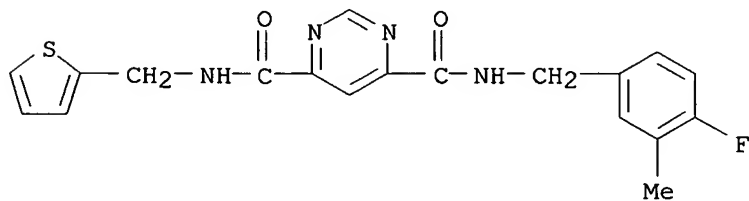
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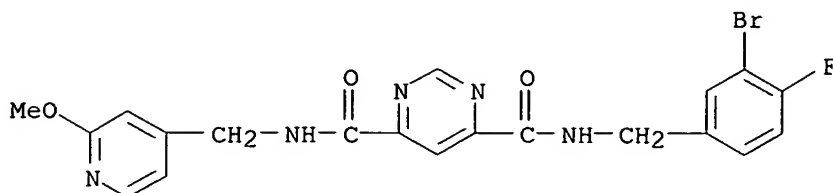
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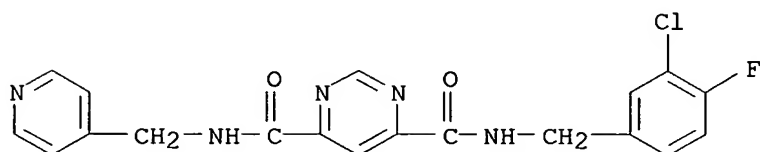
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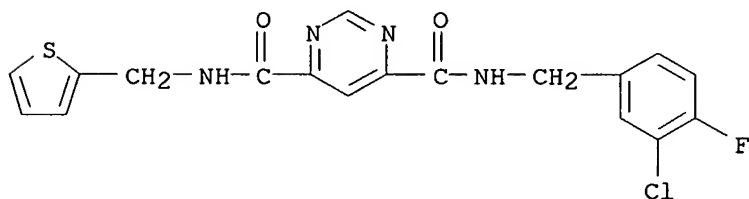
RN 720719-51-7 CAPLUS

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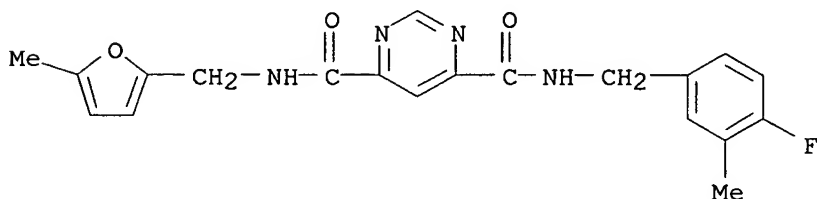
RN 720719-52-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



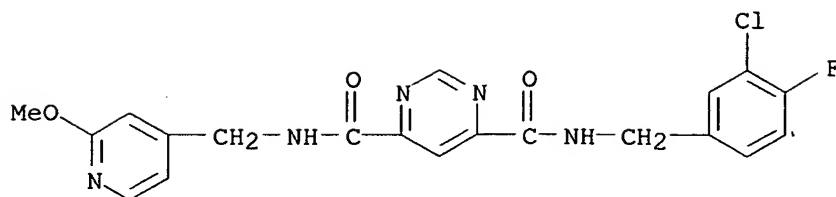
RN 720719-53-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[(5-methyl-2-furanyl)methyl]- (9CI) (CA INDEX NAME)



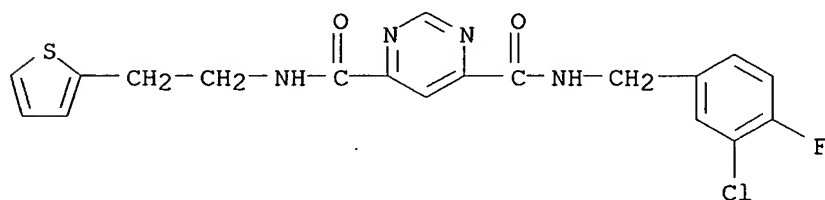
RN 720719-57-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[(2-methoxy-4-pyridinyl)methyl]- (9CI) (CA INDEX NAME)



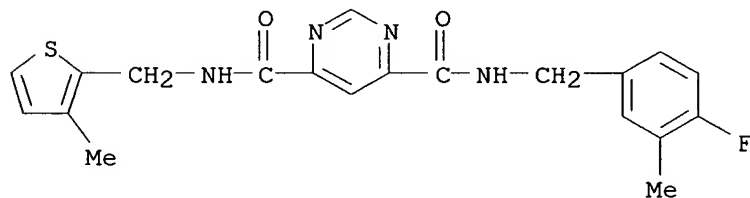
RN 720719-64-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[2-(2-thienyl)ethyl]- (9CI) (CA INDEX NAME)



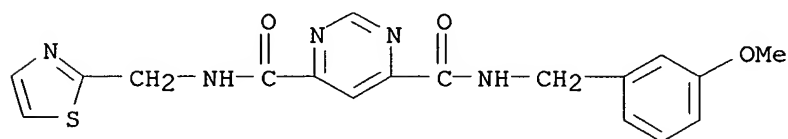
RN 720719-70-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[(3-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



RN 720719-78-8 CAPLUS

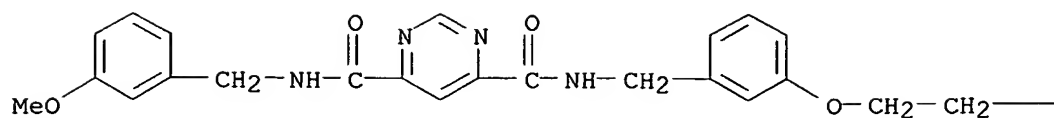
CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-(2-thiazolylmethyl)- (9CI) (CA INDEX NAME)



RN 720720-03-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[3-[2-(dimethylamino)ethoxy]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



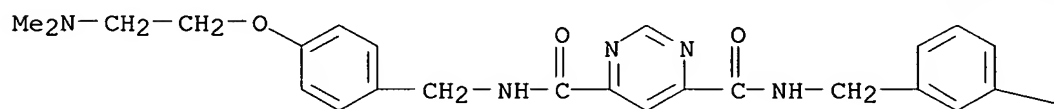
PAGE 1-B

—NMe<sub>2</sub>

RN 720720-04-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

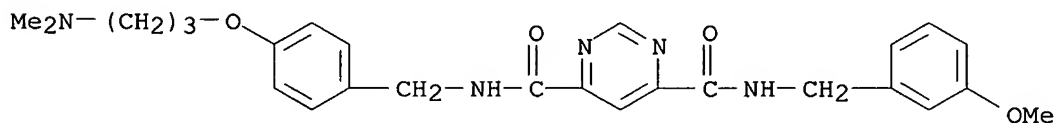


PAGE 1-B

—OMe

RN 720720-05-8 CAPLUS

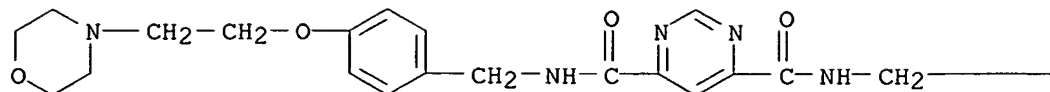
CN 4,6-Pyrimidinedicarboxamide, N-[[4-[3-(dimethylamino)propoxy]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



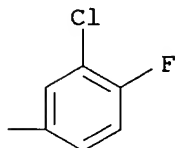
RN 720720-06-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[2-(4-morpholinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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PAGE 1-B



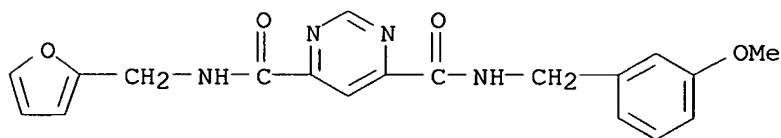
IT 720719-66-4P

RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent);  
 USES (Uses)

(preparation of pyrimidinedicarboxamides as selective MMP 13 inhibitors)

RN 720719-66-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-(2-furanylmethyl)-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



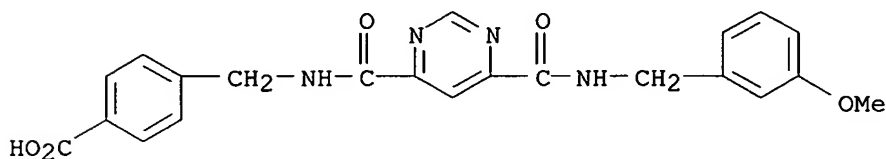
IT 448949-22-2P 691003-18-6P 691003-20-0P  
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 720719-46-0P 720719-47-1P 720719-49-3P  
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 720720-10-5P 720720-11-6P 720720-12-7P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrimidinedicarboxamides as selective MMP 13 inhibitors)

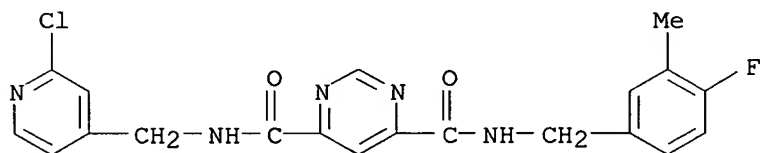
RN 448949-22-2 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



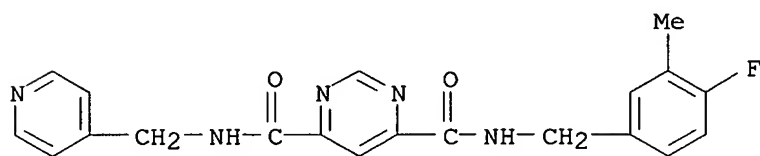
RN 691003-18-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2-chloro-4-pyridinyl)methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



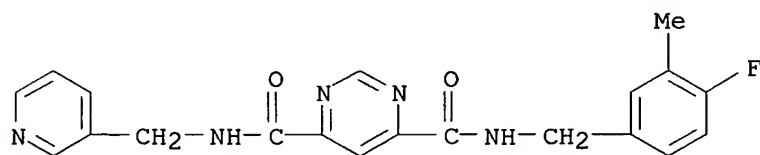
RN 691003-20-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-(4-pyridinylmethyl)- (9CI) (CA INDEX NAME)



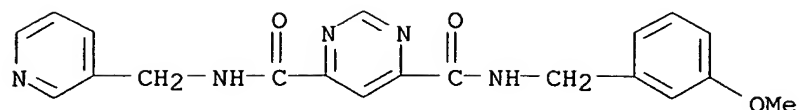
RN 691003-21-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



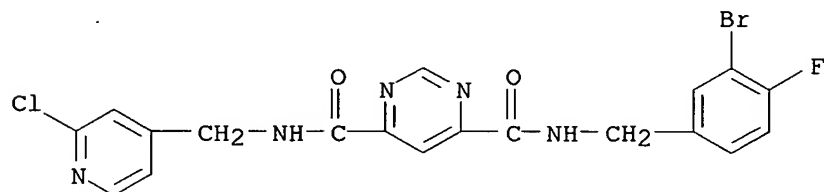
RN 691003-22-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



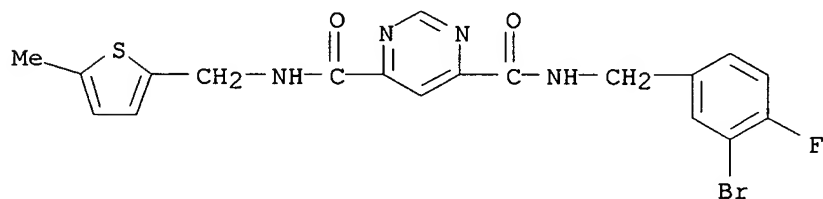
RN 720719-40-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-[(2-chloro-4-pyridinyl)methyl]- (9CI) (CA INDEX NAME)



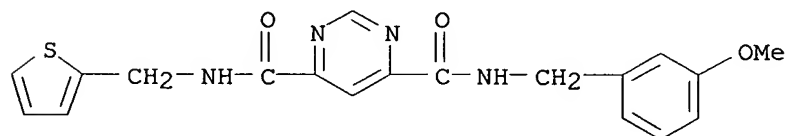
RN 720719-42-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-[(5-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



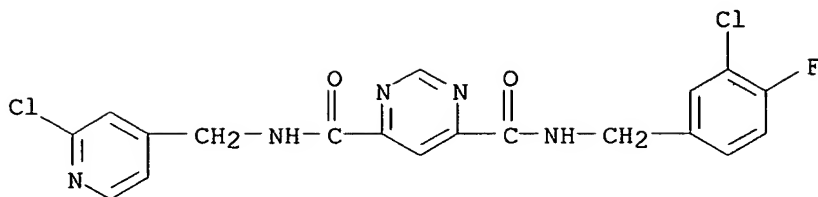
RN 720719-43-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-(2-thienylmethyl)- (9CI) (CA INDEX NAME)



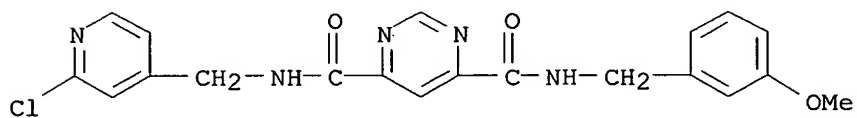
RN 720719-45-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[(2-chloro-4-pyridinyl)methyl]- (9CI) (CA INDEX NAME)



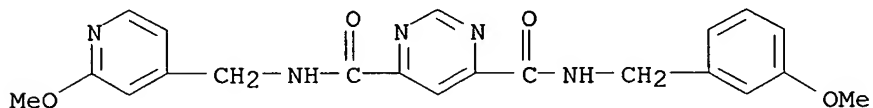
RN 720719-46-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2-chloro-4-pyridinyl)methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



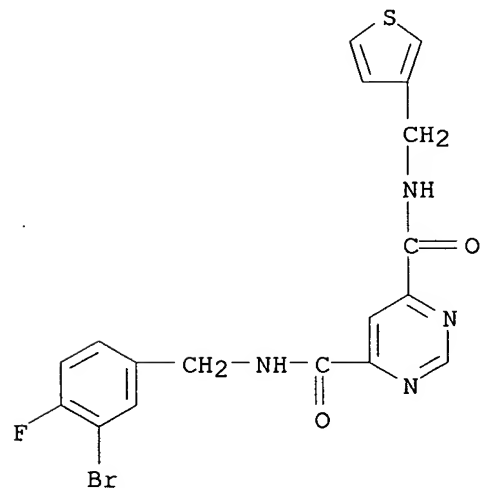
RN 720719-47-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[(2-methoxy-4-pyridinyl)methyl]- (9CI) (CA INDEX NAME)



RN 720719-49-3 CAPLUS

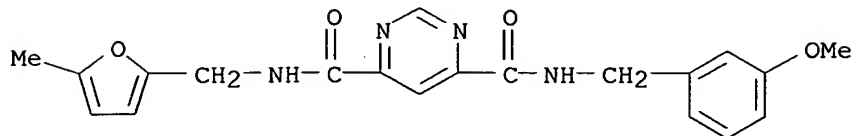
CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-[(3-thienyl)methyl]- (9CI) (CA INDEX NAME)



RN 720719-50-6 CAPLUS

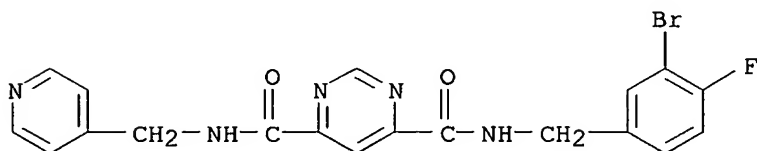
CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[(5-methyl-2-

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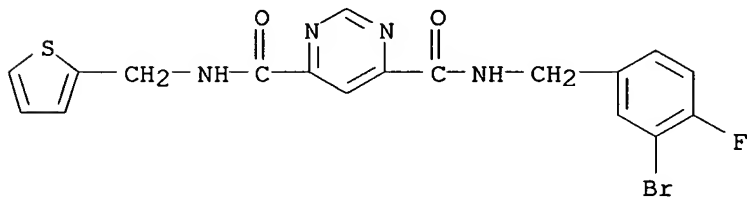
RN 720719-54-0 CAPLUS

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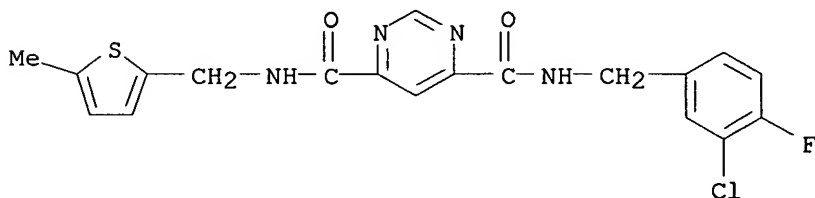
RN 720719-55-1 CAPLUS

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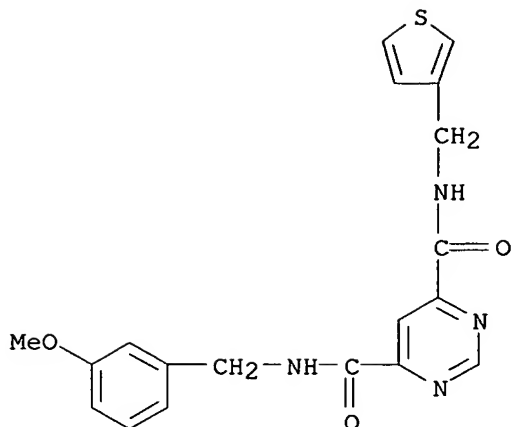
RN 720719-56-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[(5-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



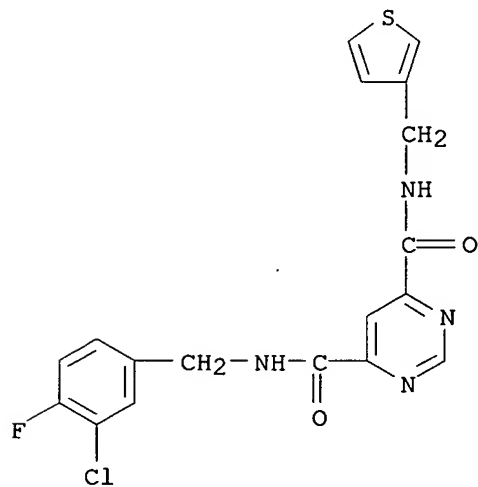
RN 720719-58-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-(3-thienylmethyl)- (9CI) (CA INDEX NAME)



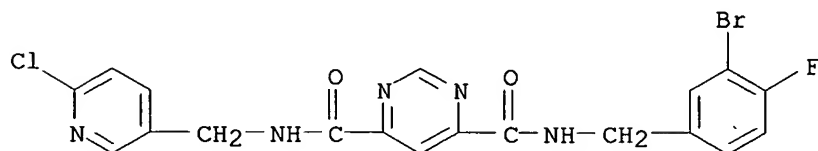
RN 720719-59-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-(3-thienylmethyl)- (9CI) (CA INDEX NAME)



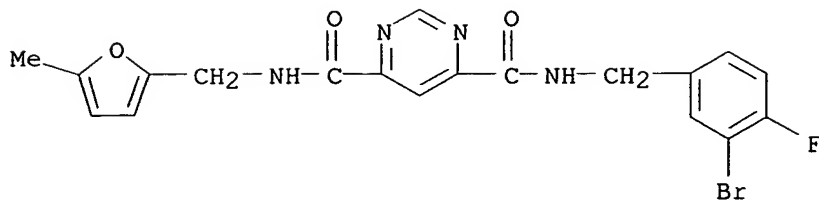
RN 720719-60-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-(6-chloro-3-pyridinyl)methyl)- (9CI) (CA INDEX NAME)



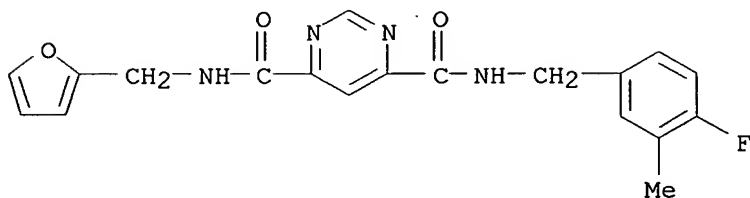
RN 720719-61-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-(5-methyl-2-furanyl)methyl)- (9CI) (CA INDEX NAME)



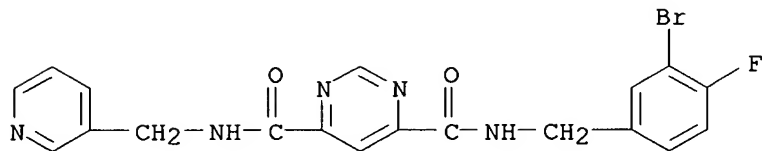
RN 720719-62-0 CAPLUS

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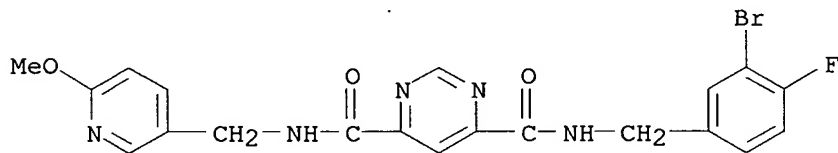
RN 720719-63-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



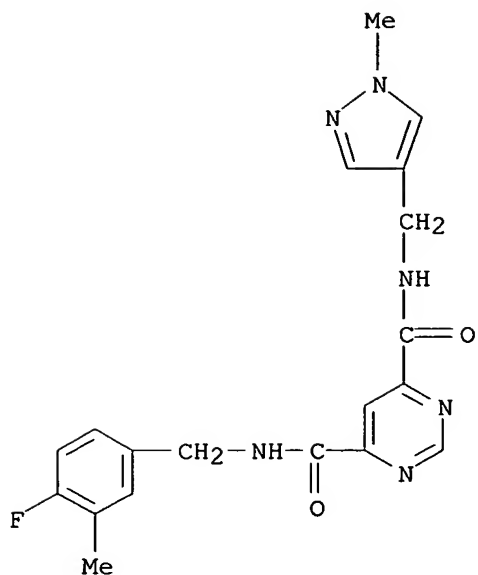
RN 720719-65-3 CAPLUS

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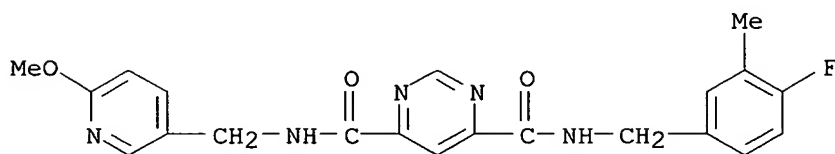
RN 720719-67-5 CAPLUS

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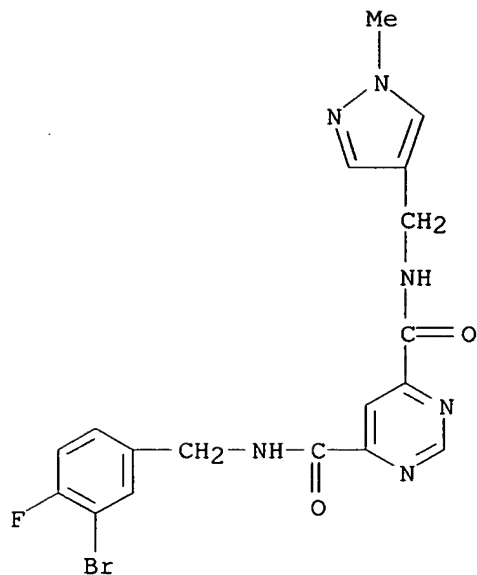
RN 720719-68-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[(6-methoxy-3-pyridinyl)methyl]- (9CI) (CA INDEX NAME)



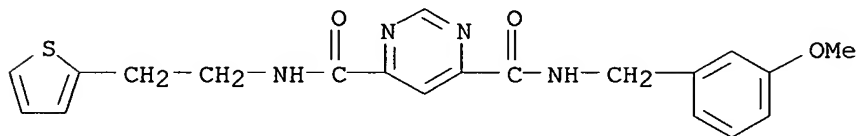
RN 720719-69-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-[(1-methyl-1H-pyrazol-4-yl)methyl]- (9CI) (CA INDEX NAME)



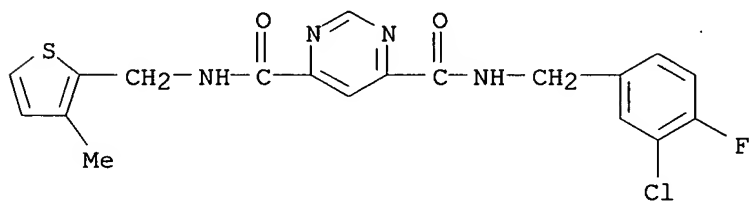
RN 720719-71-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[2-(2-thienyl)ethyl]- (9CI) (CA INDEX NAME)



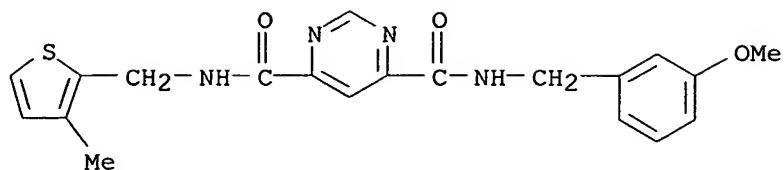
RN 720719-72-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[(3-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



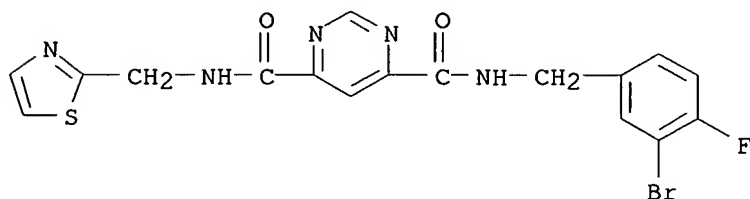
RN 720719-73-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[(3-methyl-2-thienyl)methyl]- (9CI) (CA INDEX NAME)



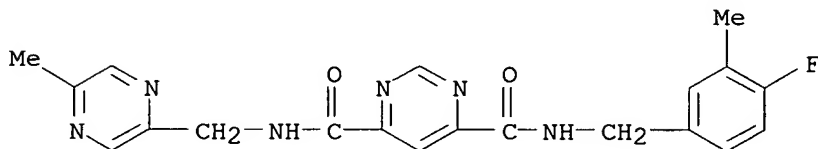
RN 720719-74-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-(2-thiazolylmethyl)- (9CI) (CA INDEX NAME)



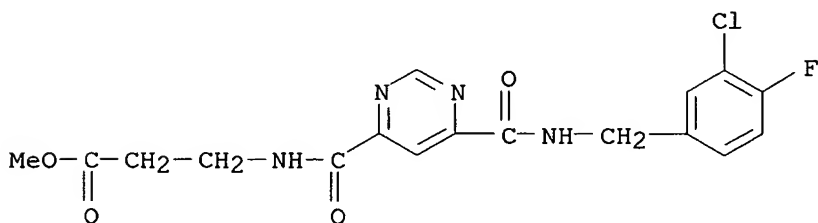
RN 720719-75-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-(5-methylpyrazinyl)methyl)- (9CI) (CA INDEX NAME)



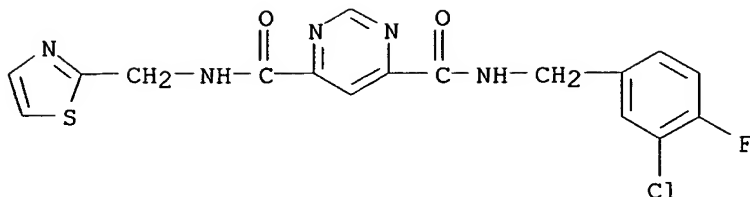
RN 720719-76-6 CAPLUS

CN  $\beta$ -Alanine, N-[[6-[[[(3-chloro-4-fluorophenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



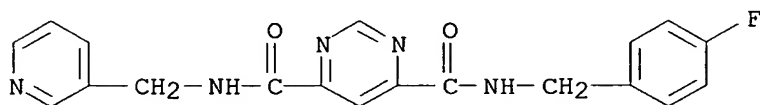
RN 720719-77-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-(2-thiazolylmethyl)- (9CI) (CA INDEX NAME)



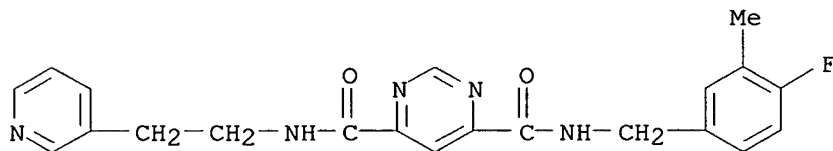
RN 720719-79-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluorophenyl)methyl]-N'-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



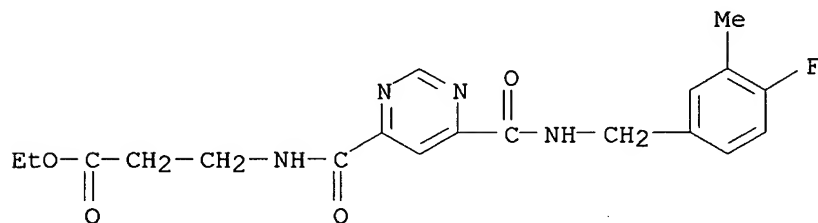
RN 720719-80-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[2-(3-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)



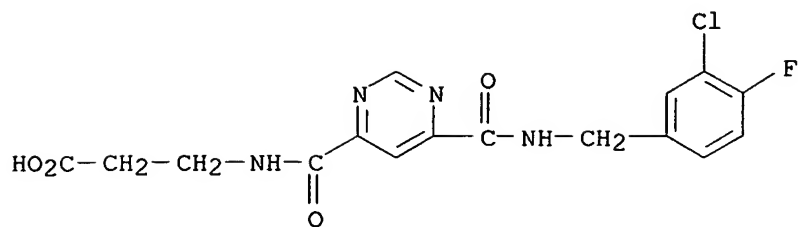
RN 720719-81-3 CAPLUS

CN  $\beta$ -Alanine, N-[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)



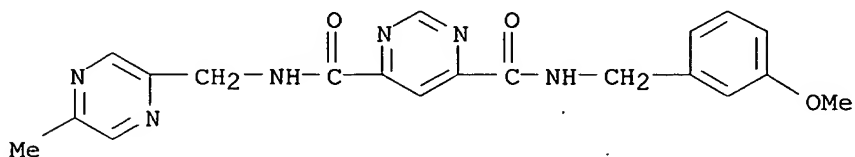
RN 720719-82-4 CAPLUS

CN  $\beta$ -Alanine, N-[[6-[[[(3-chloro-4-fluorophenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]- (9CI) (CA INDEX NAME)



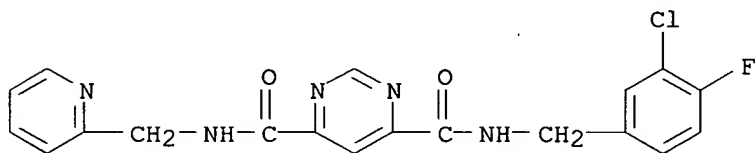
RN 720719-83-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[(5-methylpyrazinyl)methyl]- (9CI) (CA INDEX NAME)



RN 720719-84-6 CAPLUS

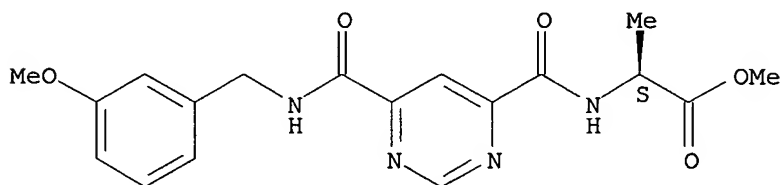
CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[(2-methylpyridinyl)methyl]- (9CI) (CA INDEX NAME)



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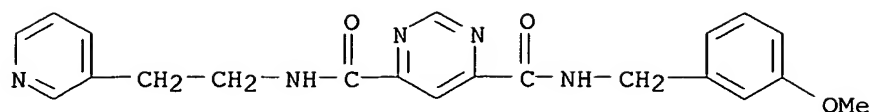
CN L-Alanine, N-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



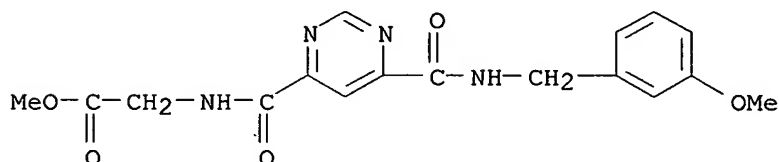
RN 720719-86-8 CAPLUS

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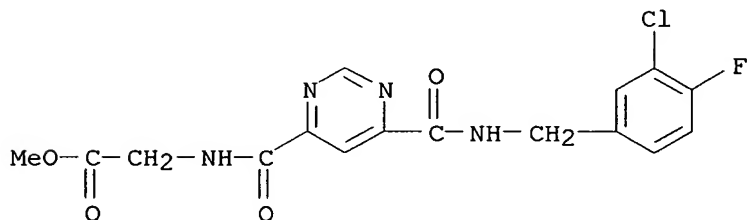
RN 720719-87-9 CAPLUS

CN Glycine, N-[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



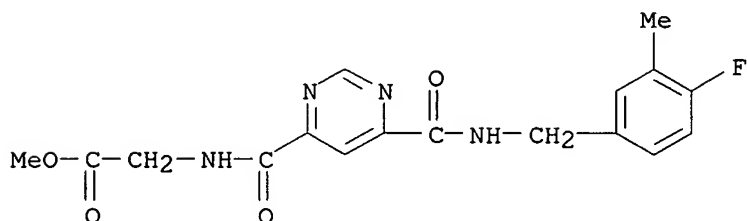
RN 720719-88-0 CAPLUS

CN Glycine, N-[[6-[[[(3-chloro-4-fluorophenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 720719-89-1 CAPLUS

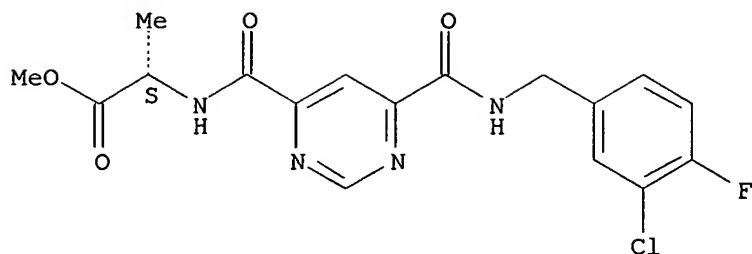
CN Glycine, N-[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



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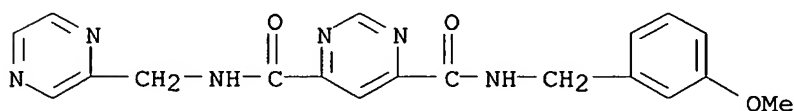
CN L-Alanine, N-[[6-[[[(3-chloro-4-fluorophenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



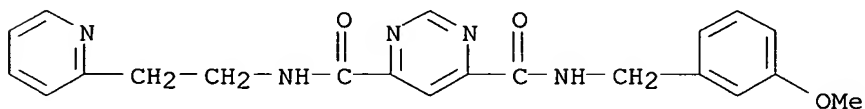
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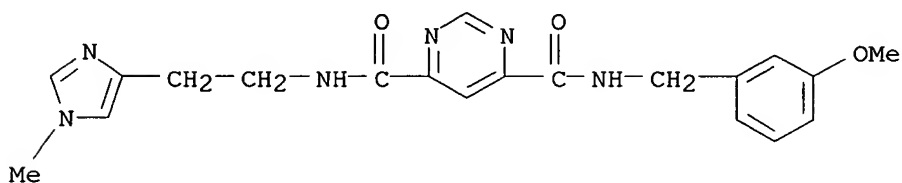
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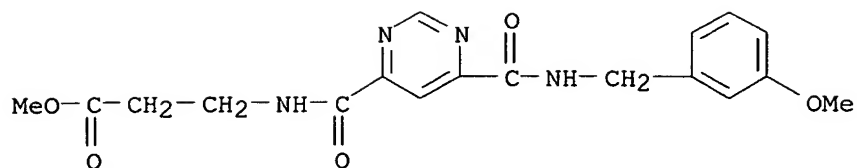
RN 720719-93-7 CAPLUS

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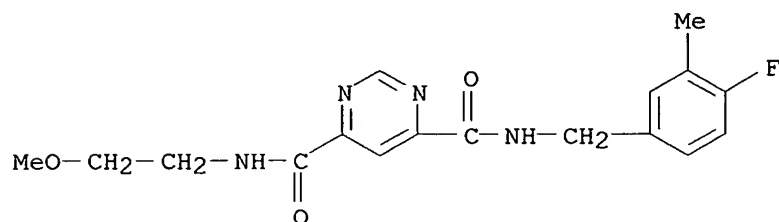
RN 720719-94-8 CAPLUS

CN  $\beta$ -Alanine, N-[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



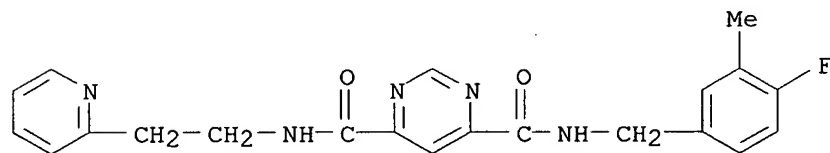
RN 720719-95-9 CAPLUS

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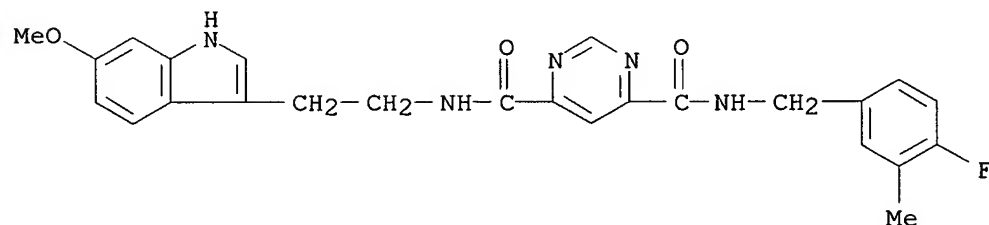
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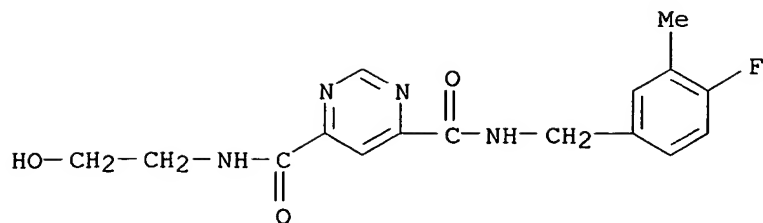
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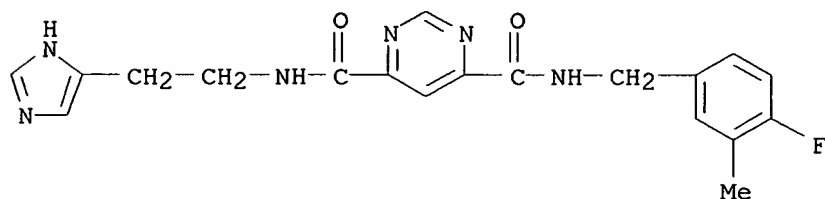
RN 720719-98-2 CAPLUS

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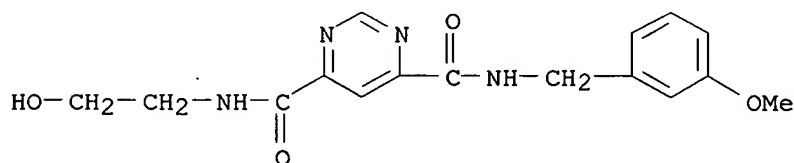
RN 720719-99-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[2-(1H-imidazol-4-yl)ethyl]- (9CI) (CA INDEX NAME)



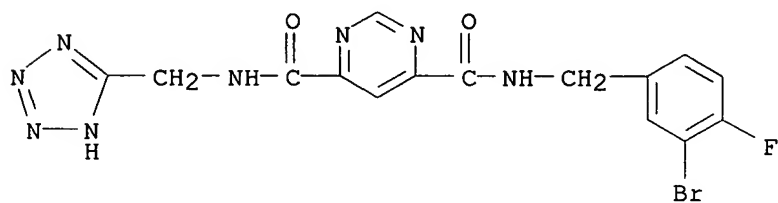
RN 720720-00-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-(2-hydroxyethyl)-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



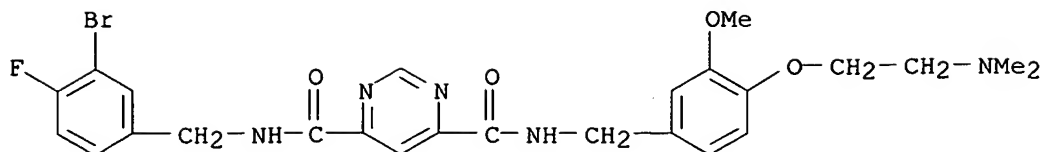
RN 720720-01-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-[4-[2-(dimethylamino)ethoxy]-3-methoxyphenyl]methyl]- (9CI) (CA INDEX NAME)



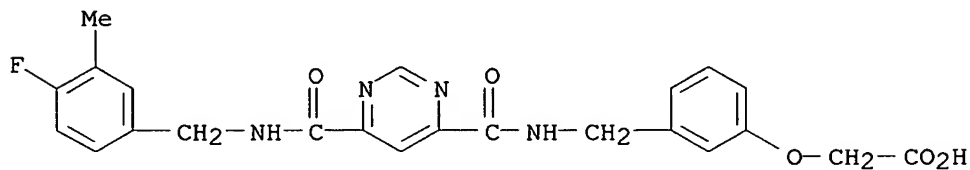
RN 720720-02-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-bromo-4-fluorophenyl)methyl]-N'-[4-[2-(dimethylamino)ethoxy]-3-methoxyphenyl]methyl]- (9CI) (CA INDEX NAME)



RN 720720-07-0 CAPLUS

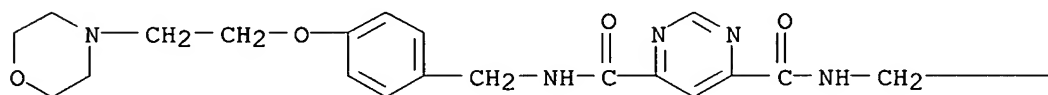
CN Acetic acid, [3-[[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenoxy]- (9CI) (CA INDEX NAME)



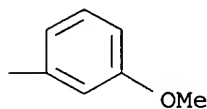
RN 720720-08-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[2-(4-morpholinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

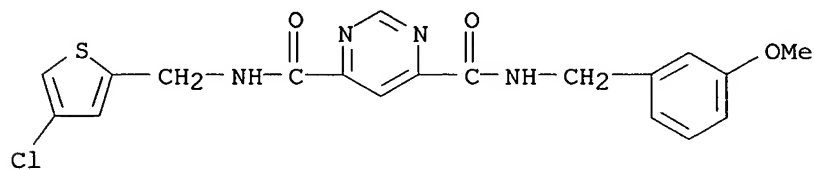


PAGE 1-B



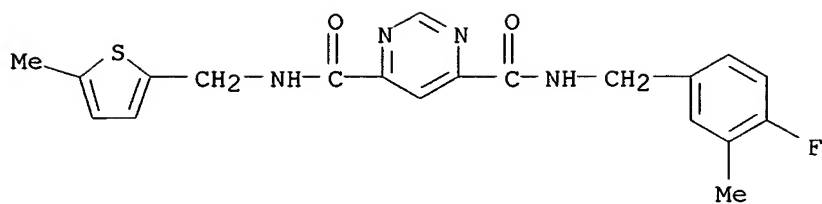
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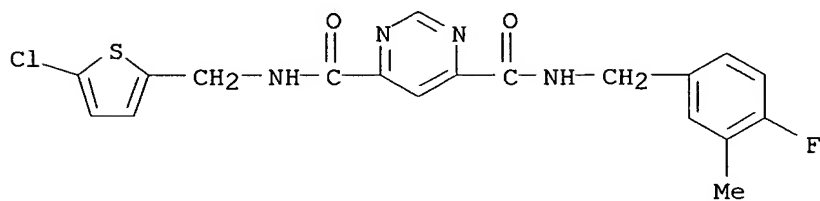
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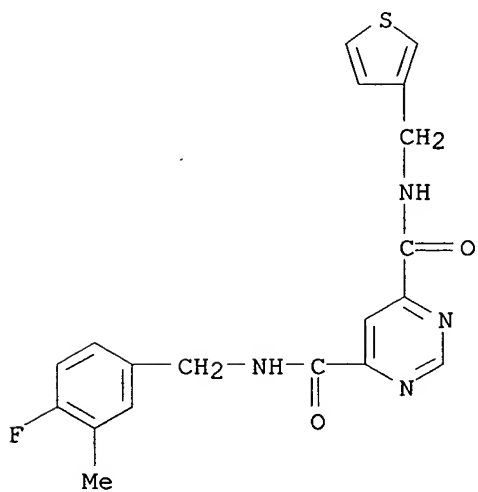
RN 720720-11-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(5-chloro-2-thienyl)methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 720720-12-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-(3-thienylmethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:412923 CAPLUS  
 DN 140:423689

TI Preparation of novel pyrimidine-4,6-dicarboxamides for the selective inhibition of collagenases

IN Klingler, Otmar; Kirsch, Reinhard; Habermann, Joerg; Weithmann, Klaus-Ulrich; Engel, Christian; Pirard, Bernard

PA Aventis Pharma Deutschland G.m.b.H., Germany

SO PCT Int. Appl., 122 pp.

CODEN: PIXXD2


DT Patent

LA German

FAN CNT 2

*Same Inv.*

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004041788	A1	20040521	WO 2003-EP11515	20031018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
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EP 1560815	A1	20050810	EP 2003-810401	20031018
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NO 2005002628	A	20050708	NO 2005-2628	20050531
PRAI DE 2002-10251019	A	20021102		
DE 2002-10254092	A	20021120		
WO 2003-EP11515	W	20031018		

*no 102(e) date!*  


OS MARPAT 140:423689

AB Pyrimidine-4,6-dicarboxamides I [R1 = H, C1-6-alkyl; R2 = (un)substituted C1-6-alkyl; R3, R4, R5, R6, R7 = H, halogen, (un)substituted C1-6-alkyl; C1-6-haloalkyl, O-(C1-6-alkyl), S-(C1-6-alkyl); R4R5, R5R6 (together to with the carbons to which they are attached) = 5- or 6-membered carbocyclic, aromatic, heterocyclic or heteroaryl ring (hetero compound containing one or more O, S or N)] are suitable for the selective inhibition of collagenase (MMP 13). Pyrimidine-4,6-dicarboxamides I can be prepared from pyrimidine-4,6-dicarboxylic acid derivs. II (Y = halogen, OH, C1-6-alkoxy; or anhydride) via reaction with R1R2NH or benzylamine III to give the monoamides IV or V, which in turn undergo reaction with benzylamine III or R1R2NH, resp. Thus, VI was prepared from di-Me pyrimidine-4,6-dicarboxylate via partial amidation with 3-MeOC6H4CH2NH2 in THF, saponification with LiOH in THF, amidation with 4-(NH2CH2)C6H4CO2Me·HCl in DMF containing TOTU and NET3, saponification with LiOH in THF and amidation with Et2NH in DMF containing TOTU

and NET3. The pyrimidine-4,6-dicarboxamides can thus be used for the treatment of degenerative joint diseases. The bioactivity of VI was determined [IC50 = 4 nM vs. MMP 13].

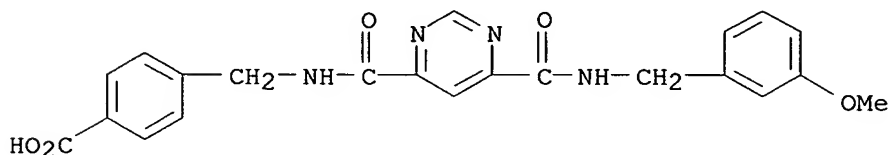
IT 448949-22-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and amidation of, by diethylamine; preparation of novel pyrimidine-4,6-dicarboxamides for the selective inhibition of collagenases)

RN 448949-22-2 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



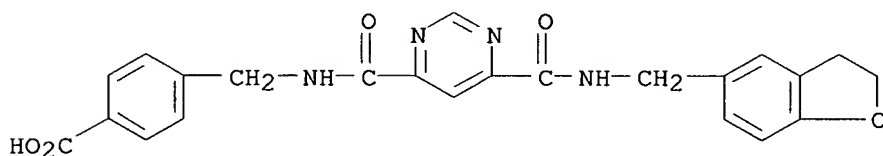
IT **691003-16-4P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and amidation of, by morpholine; preparation of novel pyrimidine-4,6-dicarboxamides for the selective inhibition of collagenases)

RN 691003-16-4 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(2,3-dihydro-5-benzofuranyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



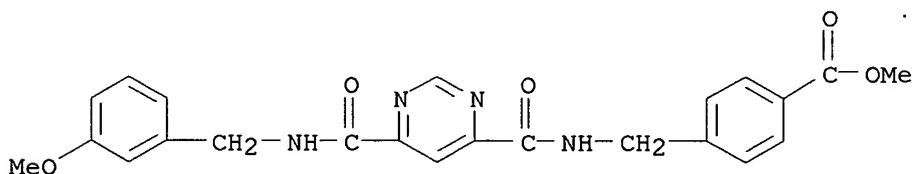
IT **448949-23-3P 691003-15-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and saponification of; preparation of novel pyrimidine-4,6-dicarboxamides for the selective inhibition of collagenases)

RN 448949-23-3 CAPLUS

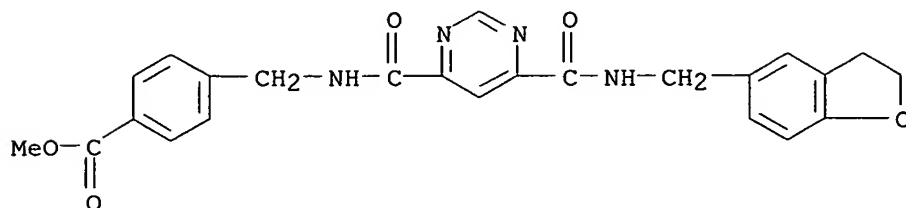
CN Benzoic acid, 4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 691003-15-3 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(2,3-dihydro-5-benzofuranyl)methyl]amino]carbonyl]

[4-pyrimidinyl]carbonyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)



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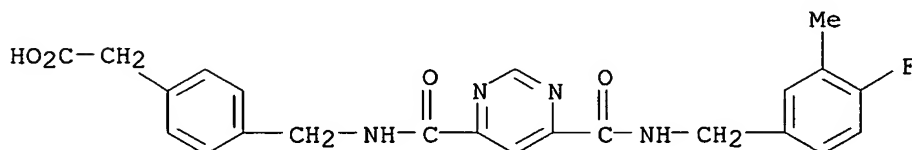
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of novel pyrimidine-4,6-dicarboxamides for the selective inhibition of collagenases)

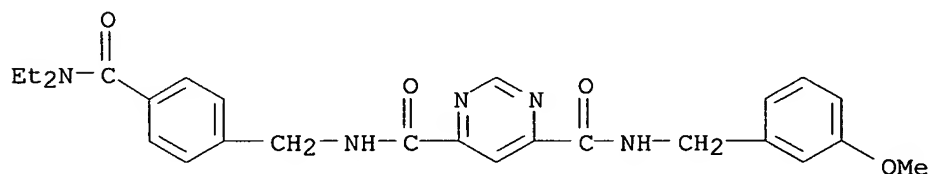
RN 690998-36-8 CAPLUS

CN Benzeneacetic acid, 4-[[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



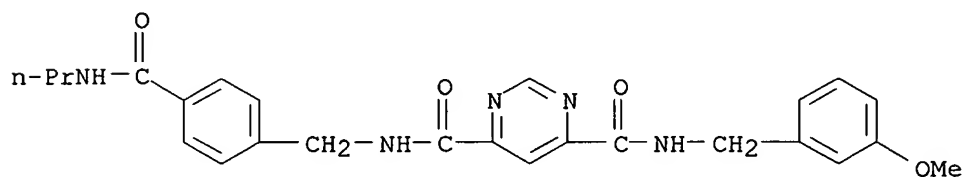
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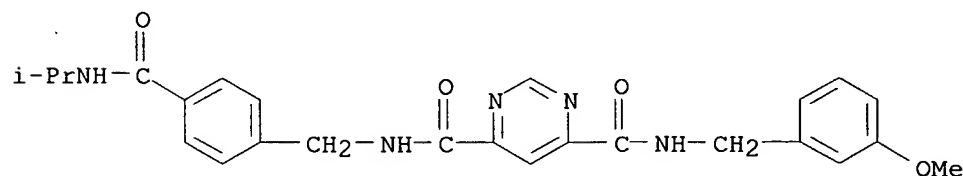
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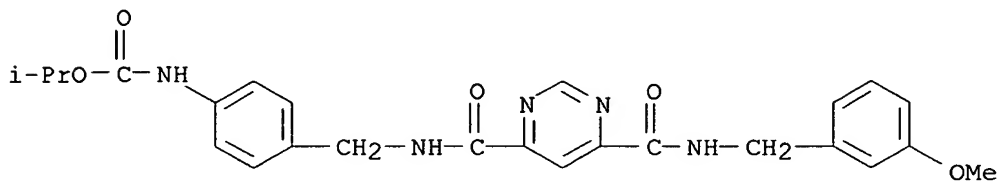
RN 690998-41-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(1-methylethyl)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



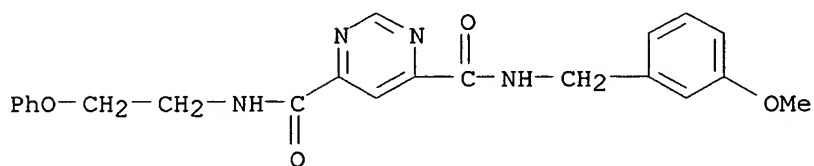
RN 690998-42-6 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



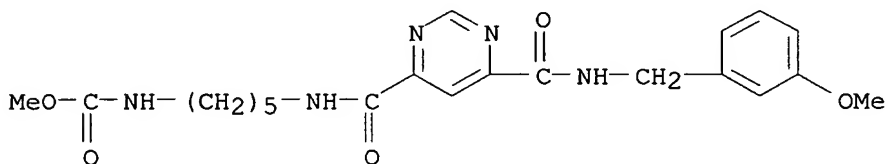
RN 690998-43-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-(2-phenoxyethyl)- (9CI) (CA INDEX NAME)



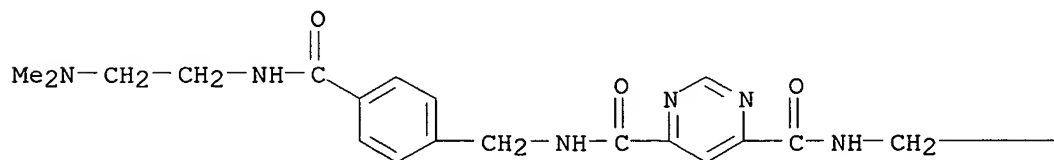
RN 690998-44-8 CAPLUS

CN Carbamic acid, [5-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]pentyl]-, methyl ester (9CI) (CA INDEX NAME)



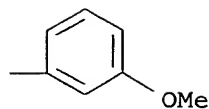
RN 690998-45-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



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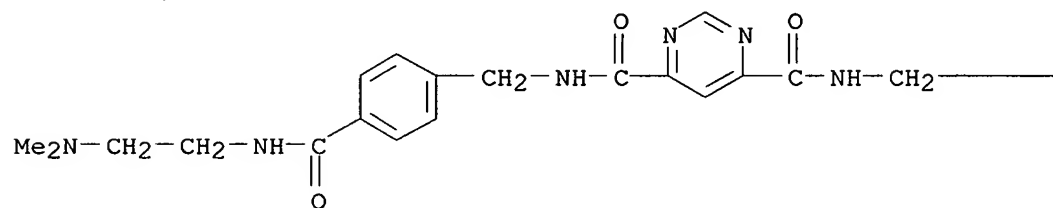
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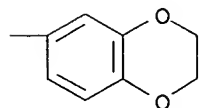
RN 690998-46-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-  
N'-[[4-[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA  
INDEX NAME)

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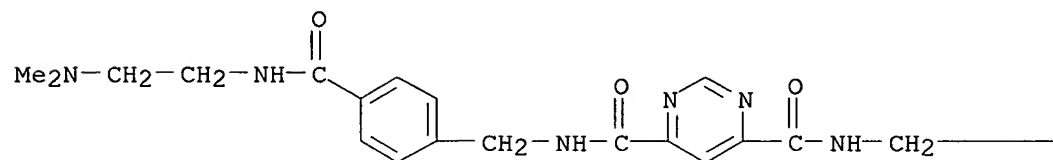
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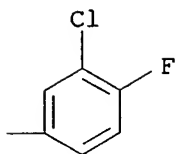


RN 690998-47-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-  
[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX  
NAME)

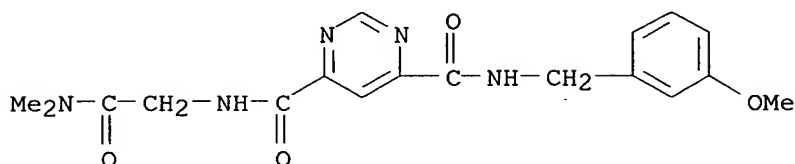
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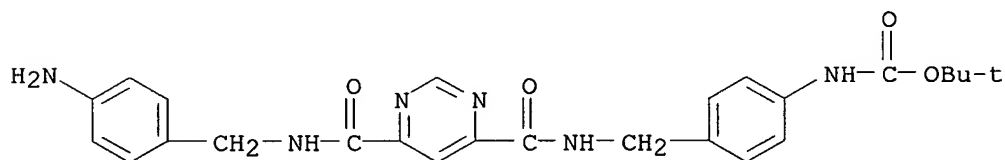
RN 690998-48-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[2-(dimethylamino)-2-oxoethyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



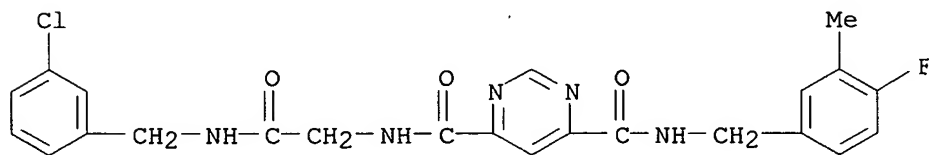
RN 690998-49-3 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(4-aminophenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



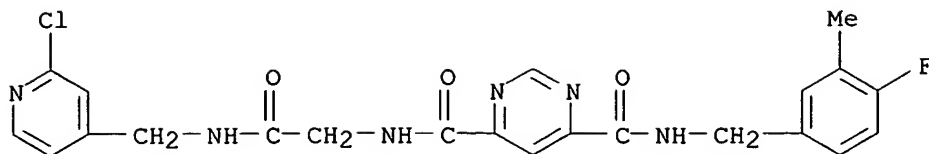
RN 690998-50-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[2-[[[(3-chlorophenyl)methyl]amino]-2-oxoethyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



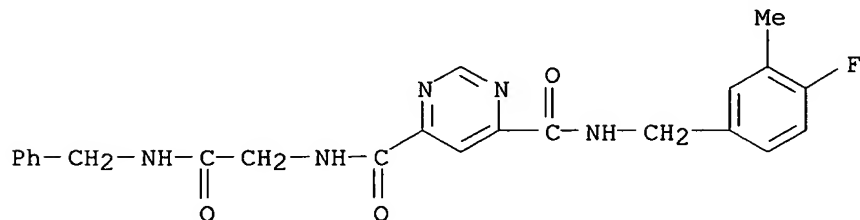
RN 690998-52-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[2-[[[(2-chloro-4-pyridinyl)methyl]amino]-2-oxoethyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



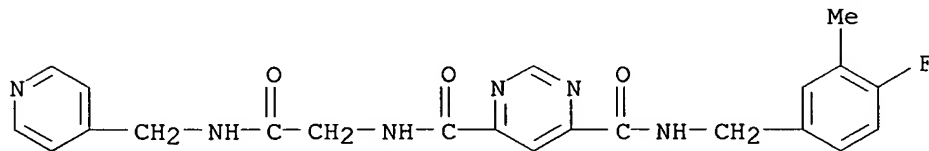
RN 690998-53-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[2-oxo-2-[(phenylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



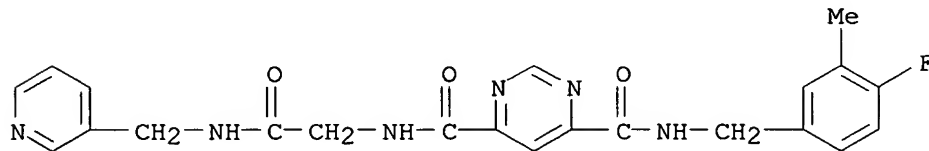
RN 690998-54-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[2-oxo-2-[(4-pyridinylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



RN 690998-55-1 CAPLUS

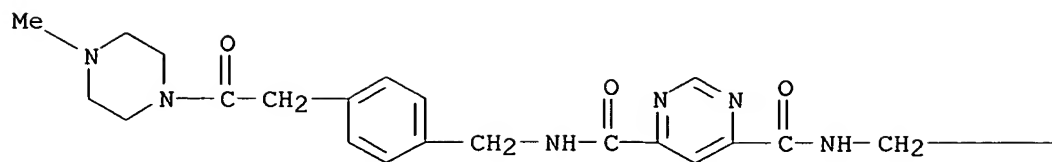
CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[2-oxo-2-[(3-pyridinylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



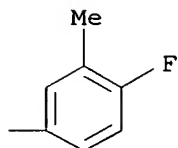
RN 690998-56-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[4-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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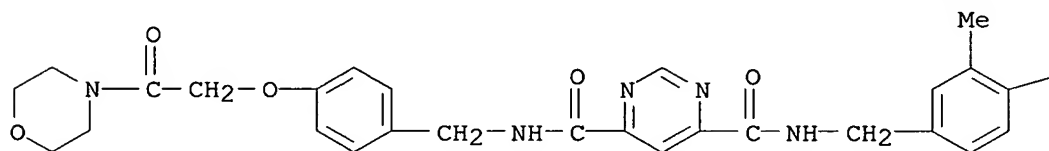
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RN 690998-57-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-(4-morpholinyl)-2-oxoethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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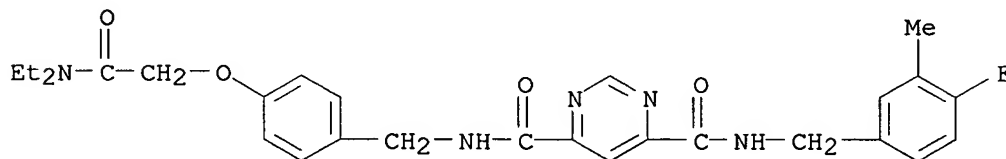


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F

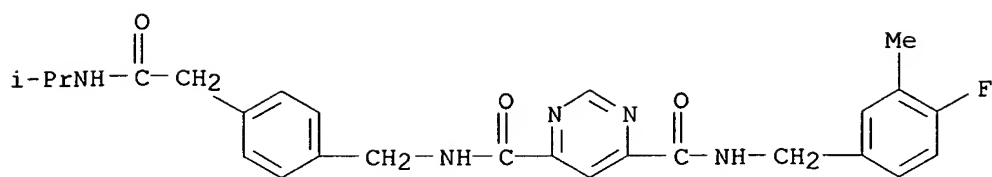
RN 690998-58-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[2-(diethylamino)-2-oxoethoxy]phenyl]methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 690998-59-5 CAPLUS

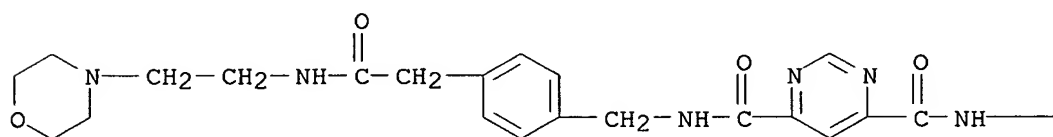
CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-[(1-methylethyl)amino]-2-oxoethyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



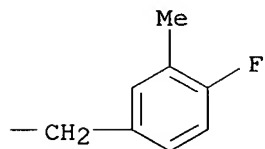
RN 690998-60-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-[[2-(4-morpholinyl)ethyl]amino]-2-oxoethyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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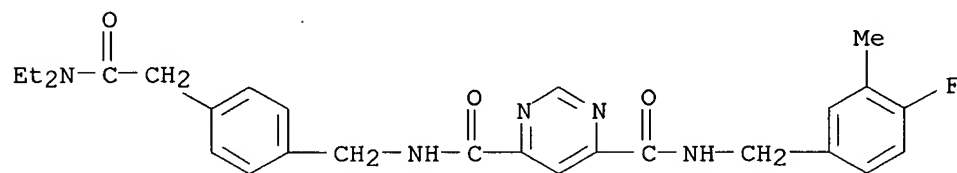


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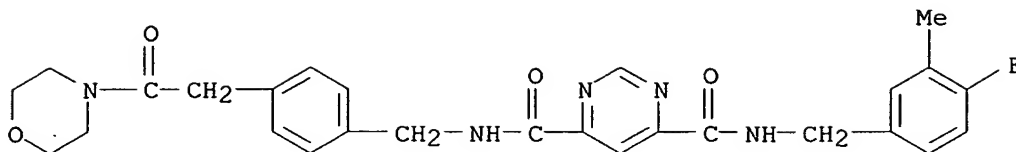
RN 690998-61-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[2-(diethylamino)-2-oxoethyl]phenyl]methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



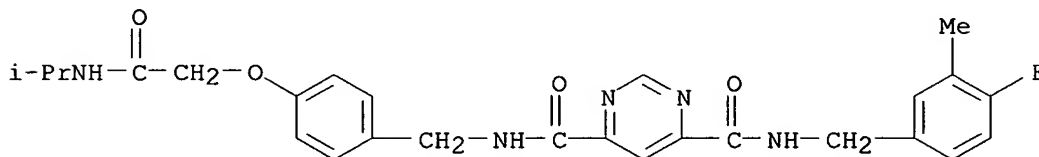
RN 690998-63-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-(4-morpholinyl)-2-oxoethyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



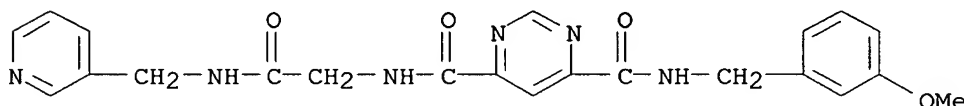
RN 690998-64-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-[(1-methylethyl)amino]-2-oxoethoxy]phenyl)methyl]- (9CI) (CA INDEX NAME)



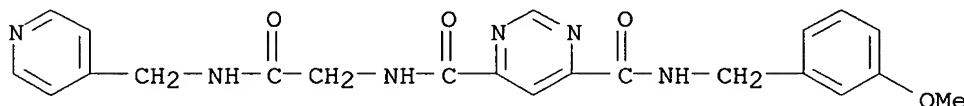
RN 690998-65-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[2-oxo-2-[(3-pyridinylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



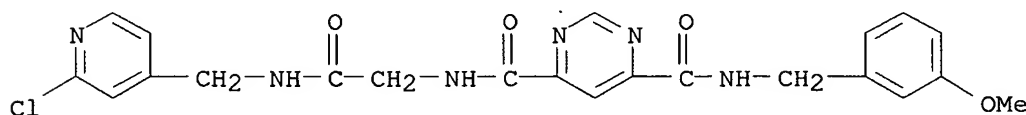
RN 690998-66-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[2-oxo-2-[(4-pyridinylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



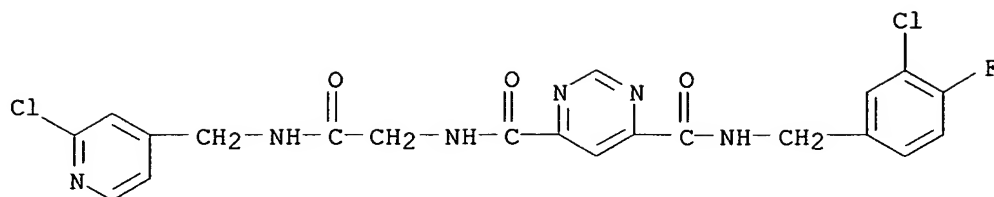
RN 690998-67-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[2-oxo-2-[(2-chloro-4-pyridinyl)methyl]amino]-2-oxoethyl]- (9CI) (CA INDEX NAME)



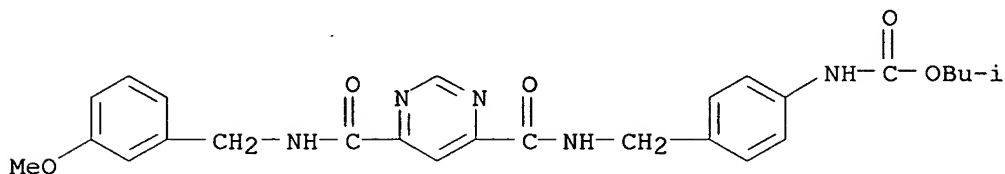
RN 690998-68-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[2-[[2-chloro-4-pyridinyl)methyl]amino]-2-oxoethyl]- (9CI) (CA INDEX NAME)



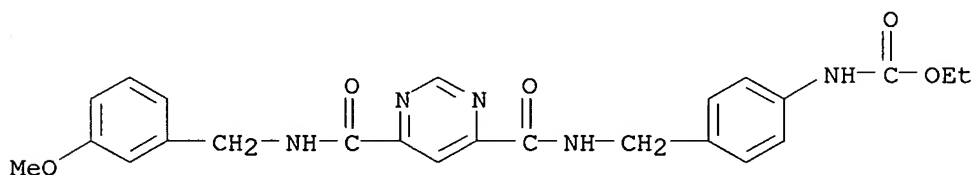
RN 690998-69-7 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)



RN 690998-70-0 CAPLUS

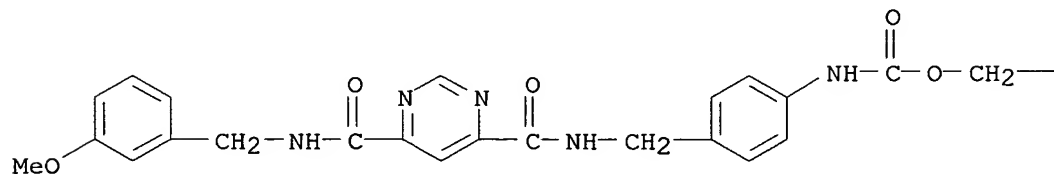
CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, ethyl ester (9CI) (CA INDEX NAME)



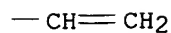
RN 690998-71-1 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)

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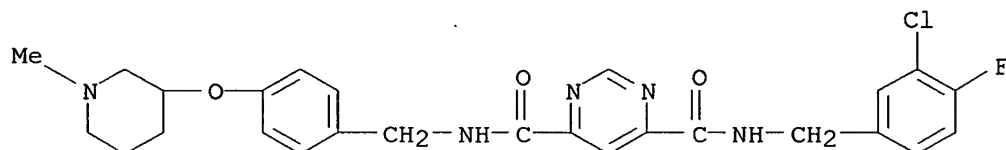


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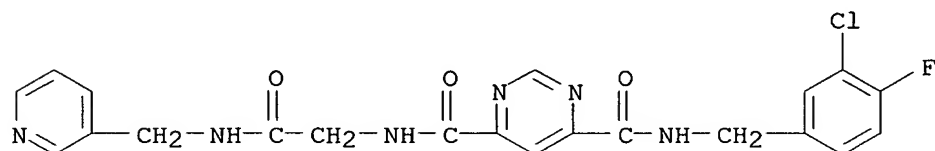
RN 690998-72-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[(1-methyl-3-piperidinyloxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 690998-73-3 CAPLUS

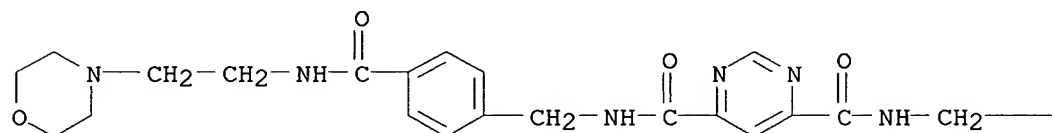
CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[2-oxo-2-[(3-pyridinylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



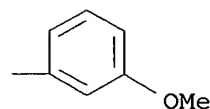
RN 690998-74-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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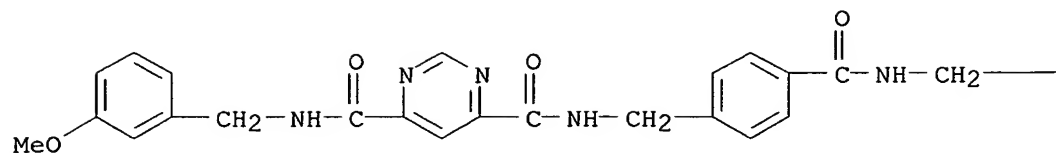
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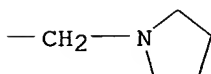
RN 690998-75-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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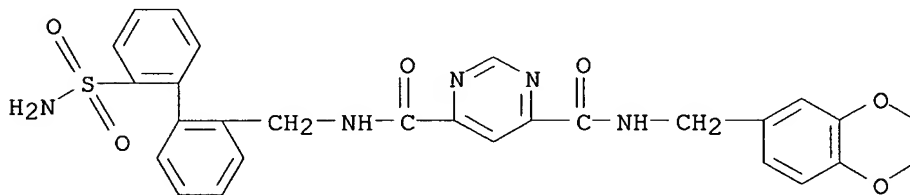


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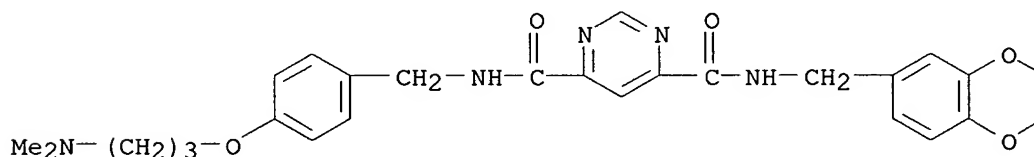
RN 691001-89-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[2'-(aminosulfonyl)[1,1'-biphenyl]-2-yl)methyl]-N'-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]- (9CI) (CA INDEX NAME)



RN 691002-10-5 CAPLUS

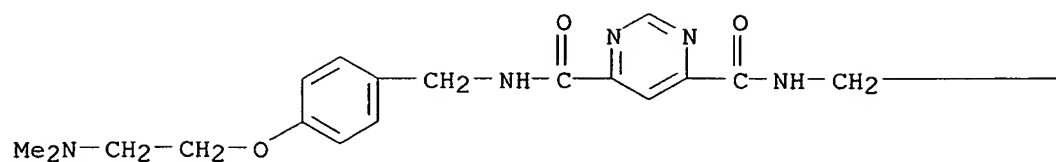
CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-N'-[[4-[3-(dimethylamino)propoxy]phenyl)methyl]- (9CI) (CA INDEX NAME)



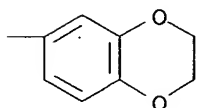
RN 691002-11-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-N'-[[4-[2-(dimethylamino)ethoxy]phenyl)methyl]- (9CI) (CA INDEX NAME)

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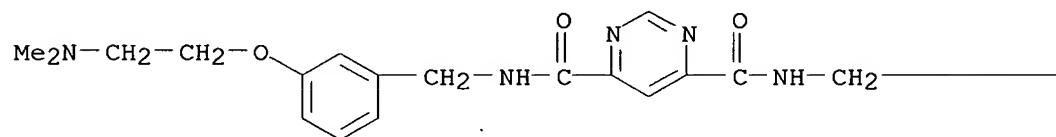
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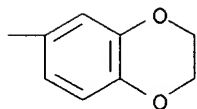
RN 691002-12-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-  
N'-[[3-[2-(dimethylamino)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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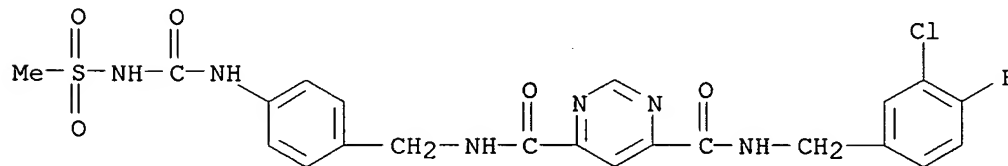


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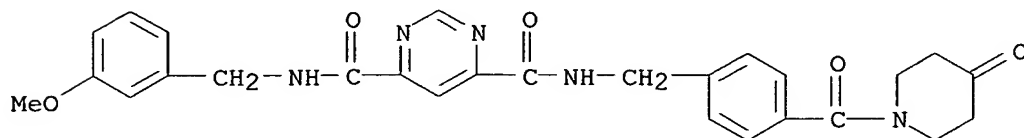
RN 691002-14-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-  
[[[(methylsulfonyl)amino]carbonyl]amino]phenyl]methyl]- (9CI) (CA INDEX  
NAME)



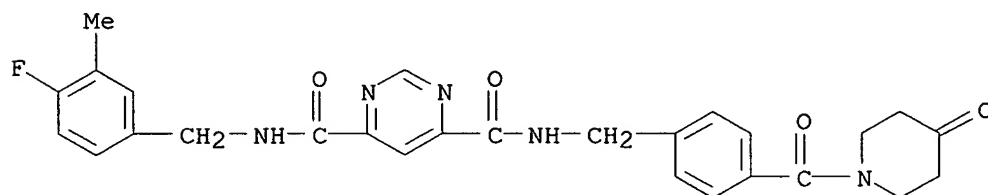
RN 691002-15-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(4-oxo-1-piperidinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



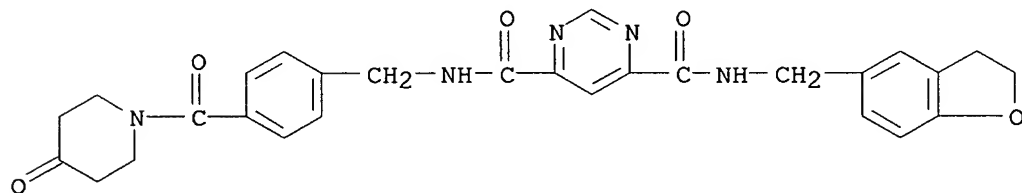
RN 691002-16-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[(4-oxo-1-piperidinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



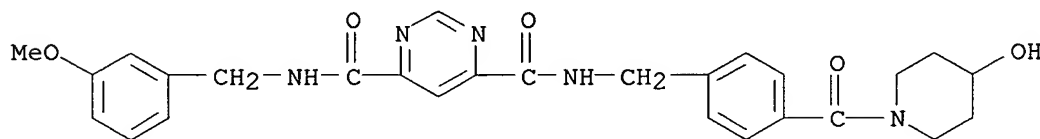
RN 691002-17-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[(4-oxo-1-piperidinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



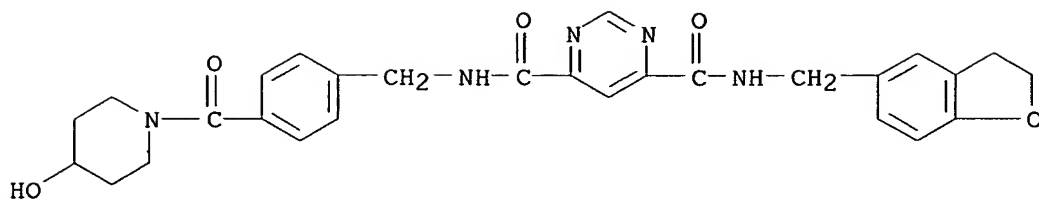
RN 691002-18-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(4-hydroxy-1-piperidinyl)carbonyl]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



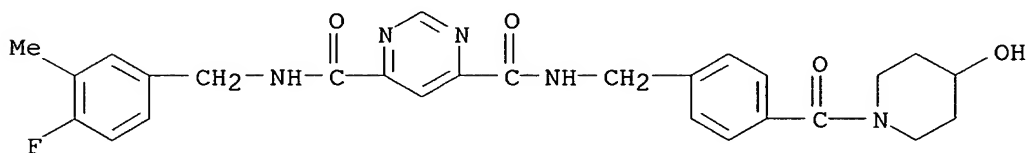
RN 691002-19-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[(4-hydroxy-1-piperidinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



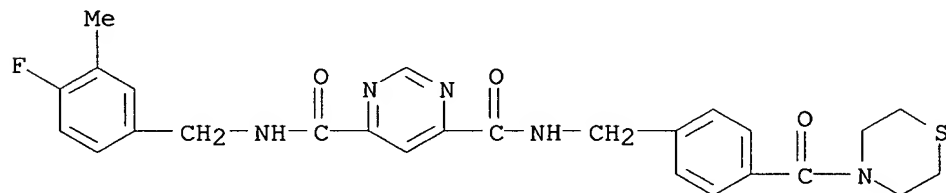
RN 691002-20-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[(4-hydroxy-1-piperidinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



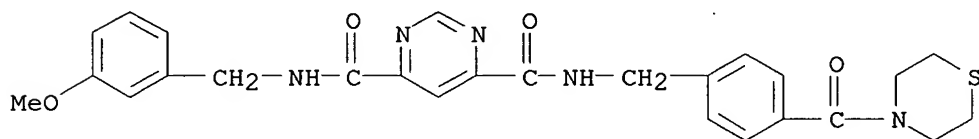
RN 691002-21-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-(4-thiomorpholinylcarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



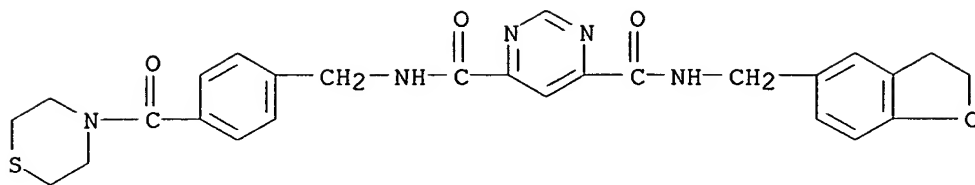
RN 691002-22-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-(4-thiomorpholinylcarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



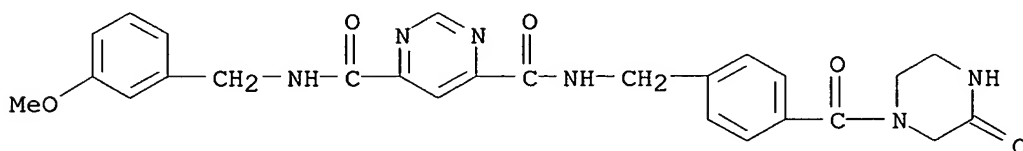
RN 691002-23-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-(4-thiomorpholinylcarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



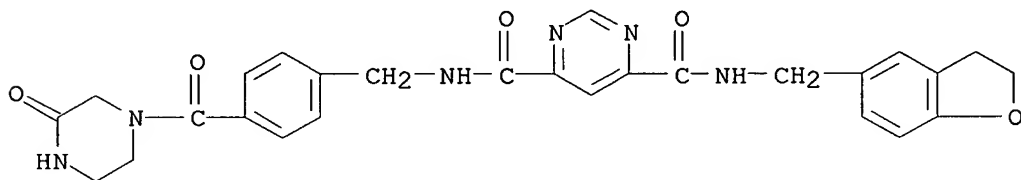
RN 691002-24-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(3-oxo-1-piperazinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



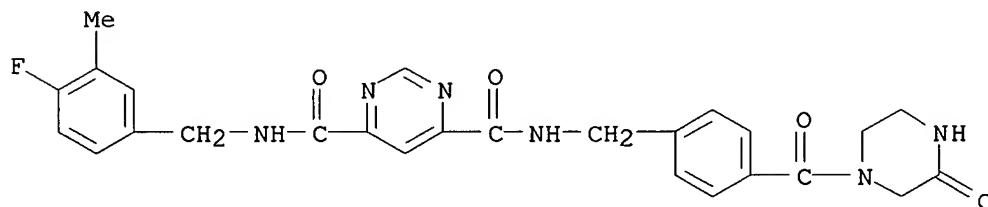
RN 691002-25-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[(3-oxo-1-piperazinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691002-26-3 CAPLUS

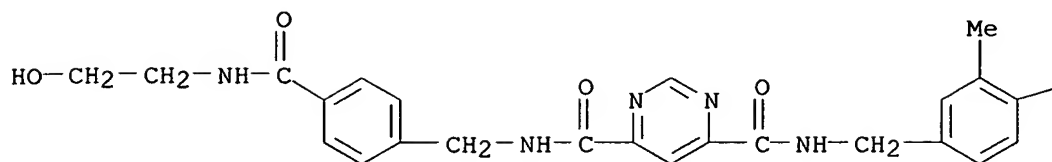
CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[(3-oxo-1-piperazinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691002-27-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[2-hydroxyethyl)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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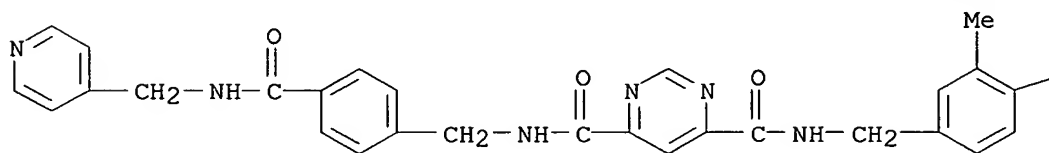
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RN 691002-28-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[4-(4-pyridinylmethyl)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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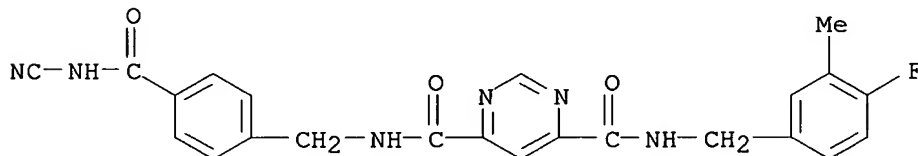


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RN 691002-29-6 CAPLUS

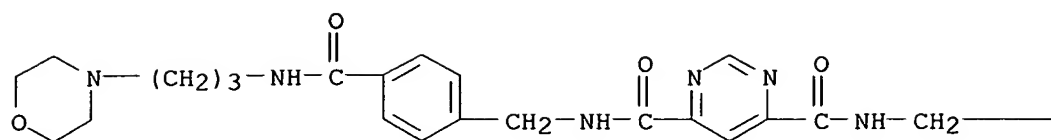
CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(cyanoamino)carbonyl]phenyl]methyl]-N'-[[4-[(4-fluoro-3-methylphenyl)methyl]methyl]- (9CI) (CA INDEX NAME)



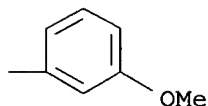
RN 691002-30-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[3-(4-morpholinyl)propyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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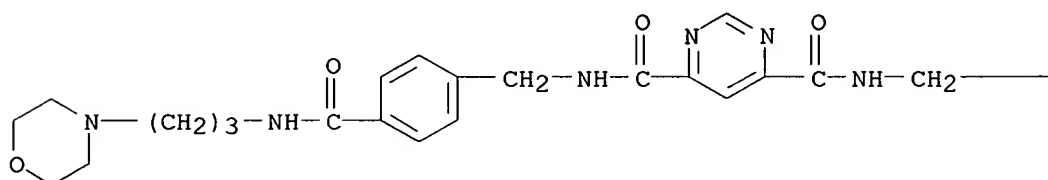
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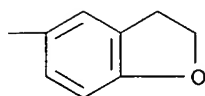
RN 691002-31-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[[[3-(4-morpholinyl)propyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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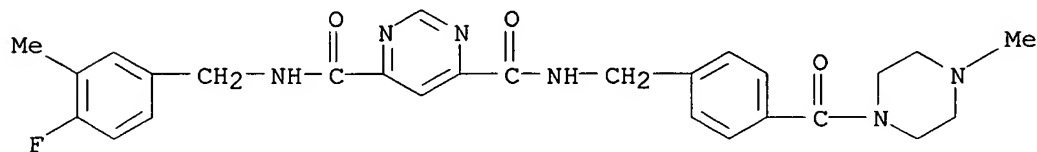


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RN 691002-32-1 CAPLUS

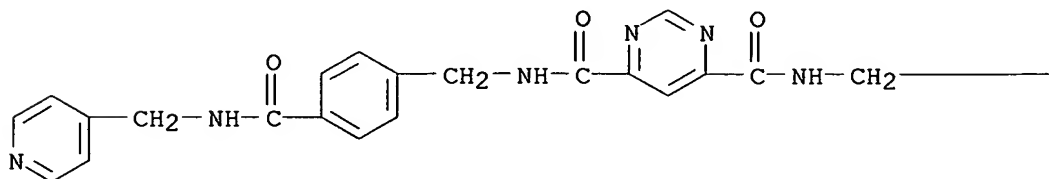
CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[(4-methyl-1-piperazinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



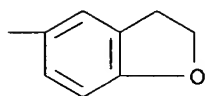
RN 691002-33-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[[4-pyridinylmethyl)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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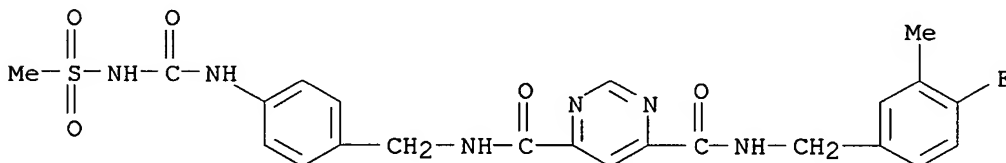


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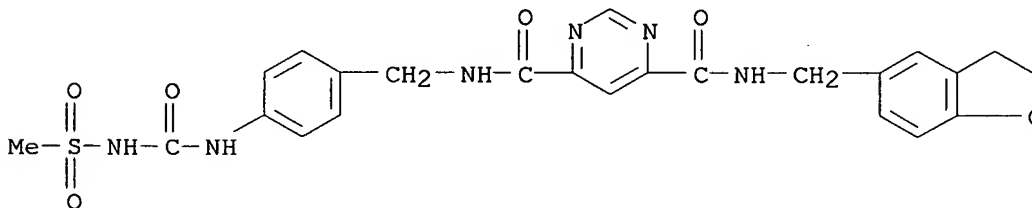
RN 691002-34-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[[(methylsulfonyl)amino]carbonyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)



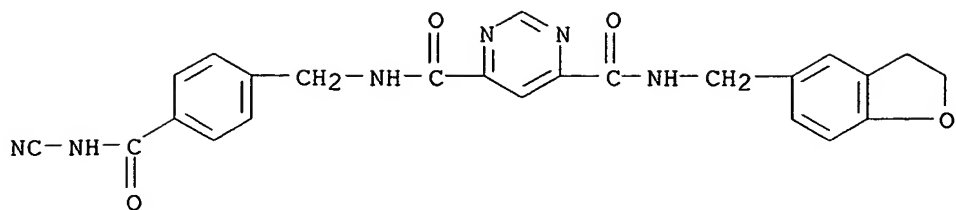
RN 691002-35-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[[[(methylsulfonyl)amino]carbonyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)



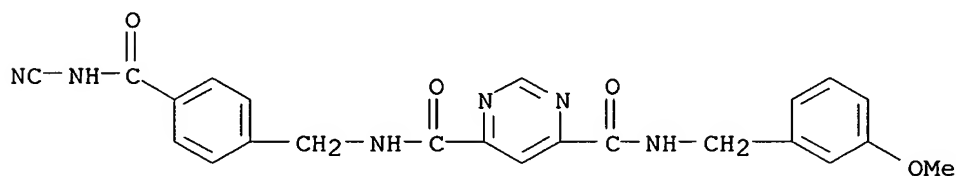
RN 691002-36-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(cyanoamino)carbonyl]phenyl]methyl]-N'-[(2,3-dihydro-5-benzofuranyl)methyl]- (9CI) (CA INDEX NAME)



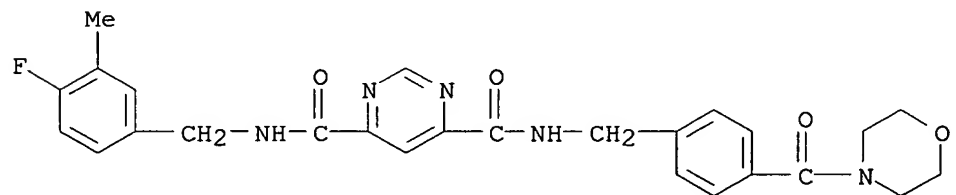
RN 691002-37-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(cyanoamino)carbonyl]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



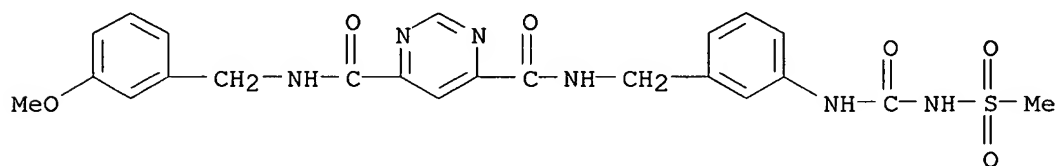
RN 691002-38-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-(4-morpholinylcarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



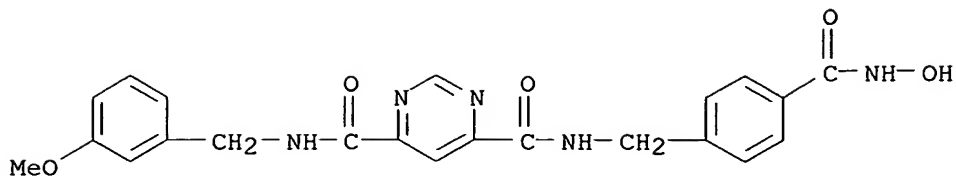
RN 691002-39-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[3-[[[(methylsulfonyl)amino]carbonyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691002-40-1 CAPLUS

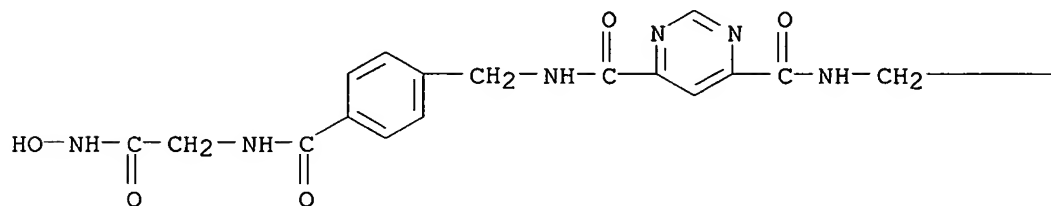
CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(hydroxyamino)carbonyl]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



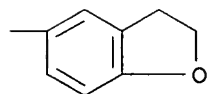
RN 691002-41-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[[[2-(hydroxyamino)-2-oxoethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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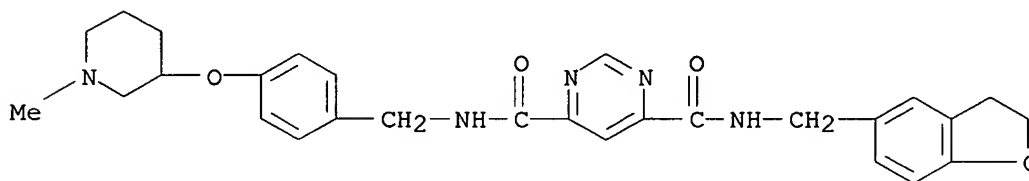


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RN 691002-42-3 CAPLUS

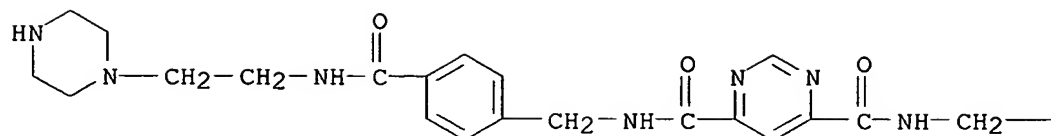
CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[[[2-(1-methyl-3-piperidinyloxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



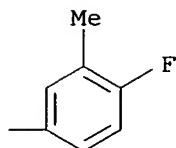
RN 691002-43-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[[2-(1-piperazinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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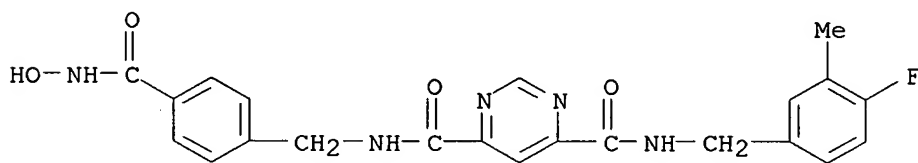


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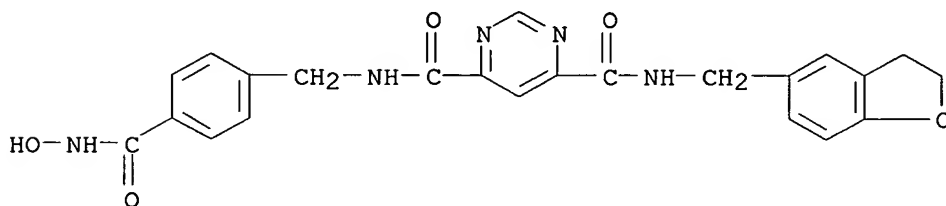
RN 691002-44-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[(hydroxyamino)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



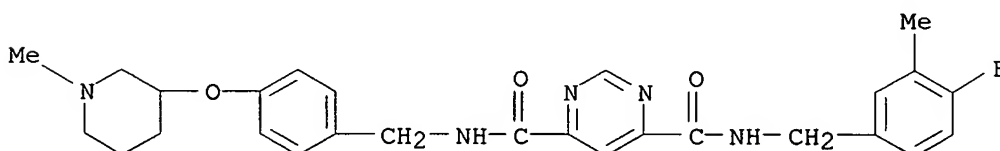
RN 691002-45-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[(hydroxyamino)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



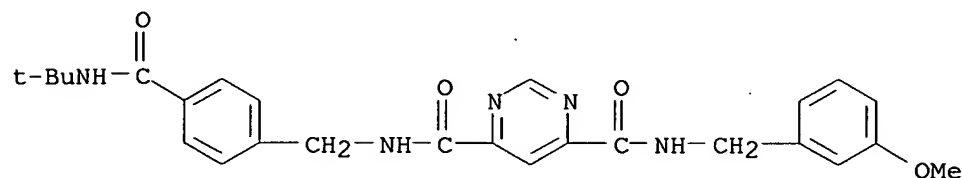
RN 691002-46-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[(1-methyl-3-piperidinyl)oxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



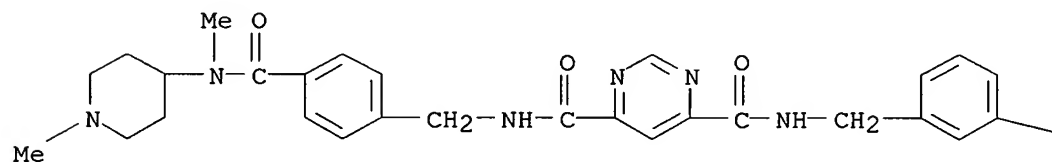
RN 691002-47-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[(1,1-dimethylethyl)amino]carbonyl]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 691002-48-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[methyl(1-methyl-4-piperidiny)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



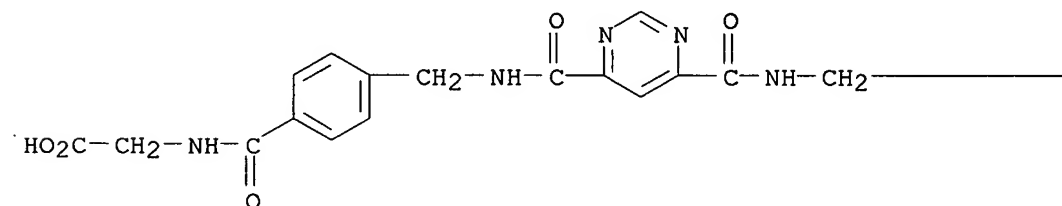
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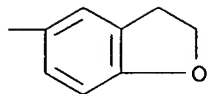
RN 691002-49-0 CAPLUS

CN Glycine, N-[4-[[[6-[[[(2,3-dihydro-5-benzofuranyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]benzoyl]- (9CI) (CA INDEX NAME)



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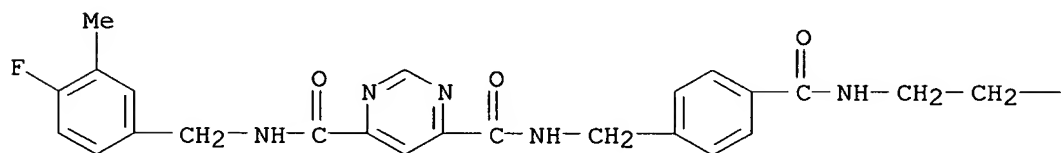
PAGE 1-B



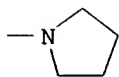
RN 691002-50-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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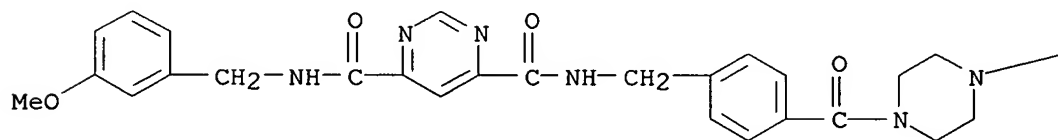
PAGE 1-B



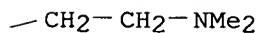
RN 691002-51-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[4-[2-(dimethylamino)ethyl]-1-piperazinyl]carbonyl]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

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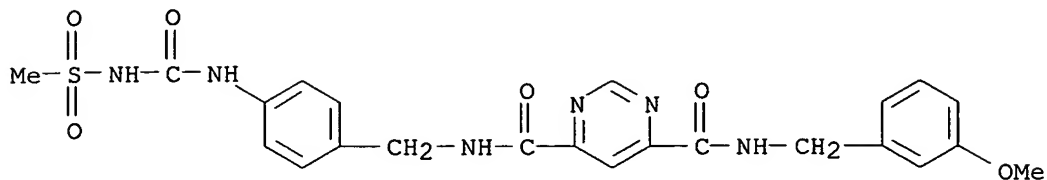
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RN 691002-52-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-

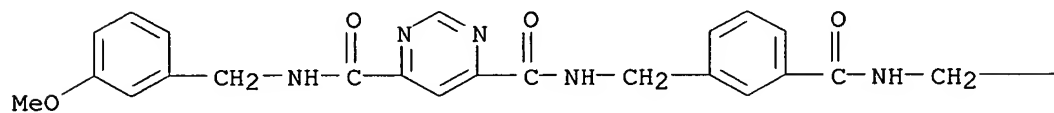
[[[(methylsulfonyl)amino]carbonyl]amino]phenyl)methyl]- (9CI) (CA INDEX NAME)



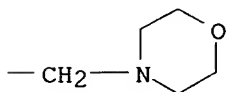
RN 691002-53-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[3-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl)methyl]- (9CI) (CA INDEX NAME)

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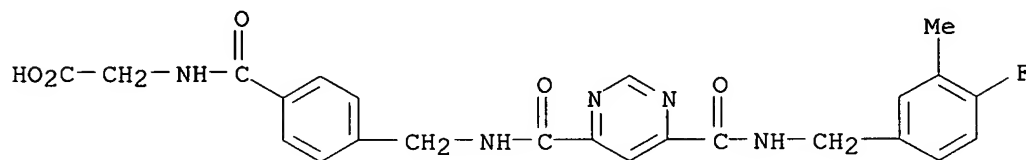


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RN 691002-54-7 CAPLUS

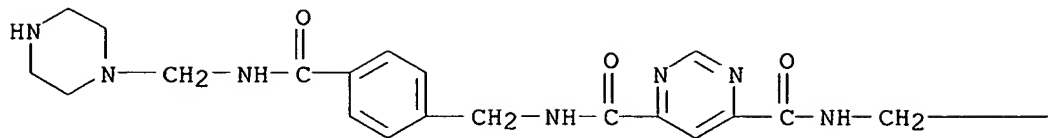
CN Glycine, N-[4-[[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]benzoyl]- (9CI) (CA INDEX NAME)



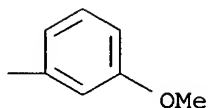
RN 691002-55-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[1-piperazinylmethyl]amino]carbonyl]phenyl)methyl]- (9CI) (CA INDEX NAME)

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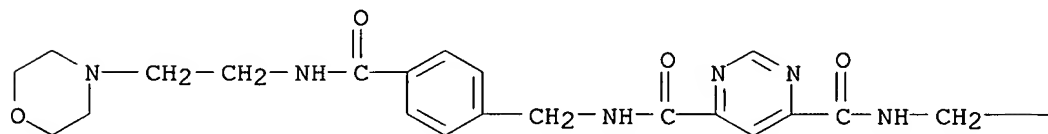
PAGE 1-B



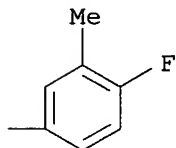
RN 691002-56-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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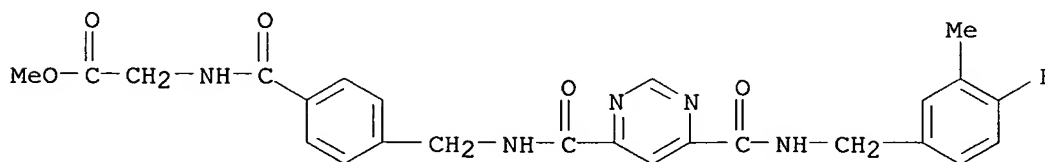


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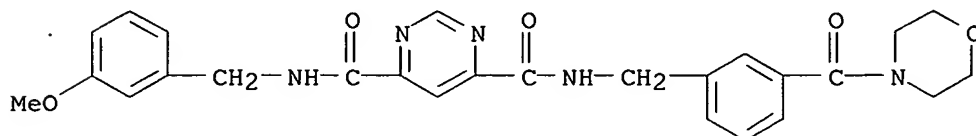
RN 691002-57-0 CAPLUS

CN Glycine, N-[4-[[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]benzoyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 691002-58-1 CAPLUS

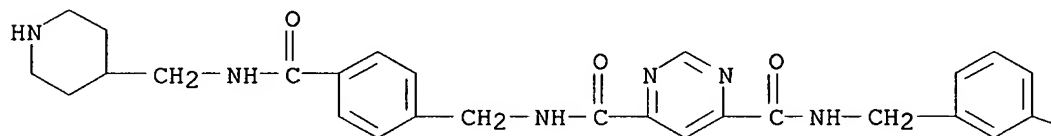
CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[3-(4-morpholinylcarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691002-59-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(4-piperidinylmethyl)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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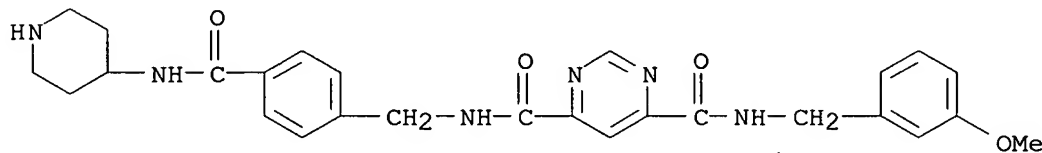


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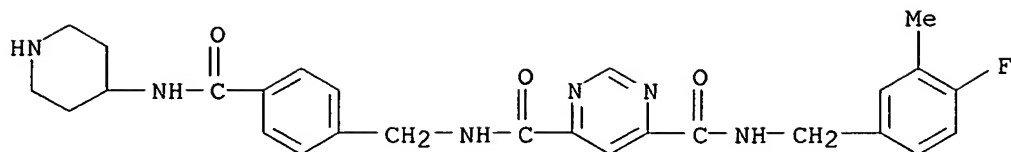
RN 691002-60-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(4-piperidinylamino)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



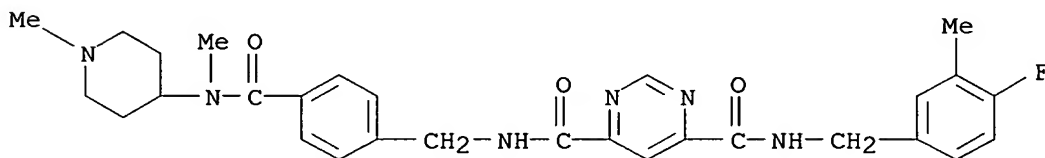
RN 691002-61-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[(4-piperidinylamino)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



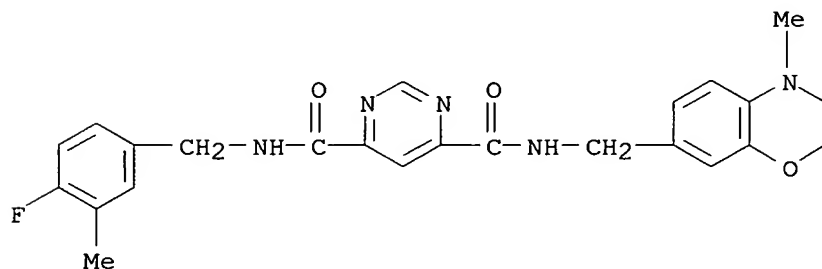
RN 691002-62-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[methyl(1-methyl-4-piperidiny)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691002-63-8 CAPLUS

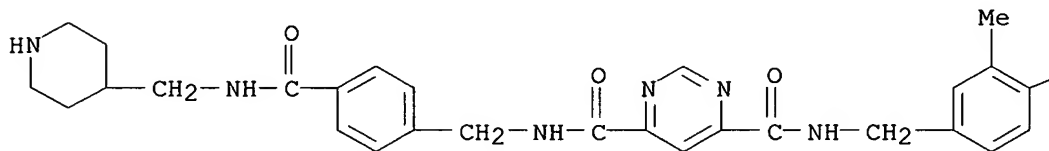
CN 4,6-Pyrimidinedicarboxamide, N-[(3,4-dihydro-4-methyl-2H-1,4-benzoxazin-7-yl)methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 691002-64-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[[4-piperidiny)methyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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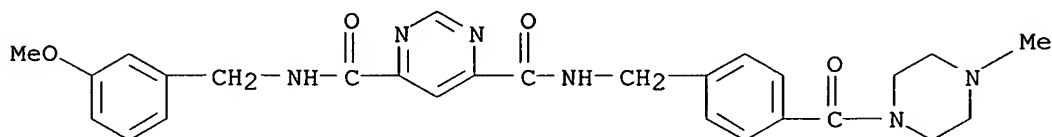


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RN 691002-65-0 CAPLUS

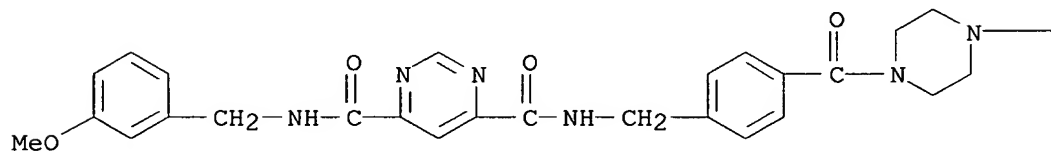
CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(4-methyl-1-piperazinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



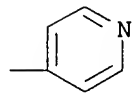
RN 691002-66-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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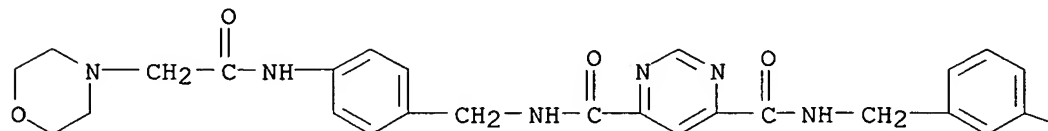
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RN 691002-67-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(4-morpholinylacetyl)amino]phenyl]methyl]- (9CI) (CA INDEX NAME)

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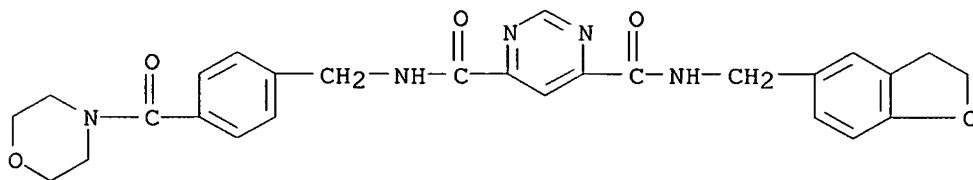


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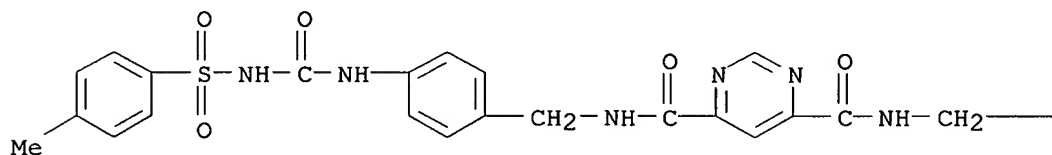
RN 691002-68-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-(4-morpholinylcarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



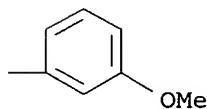
RN 691002-69-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)



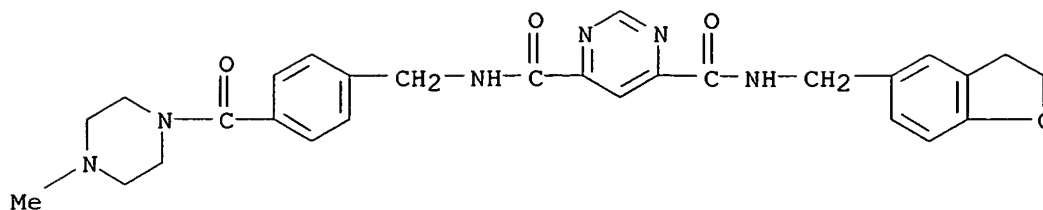
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RN 691002-70-7 CAPLUS

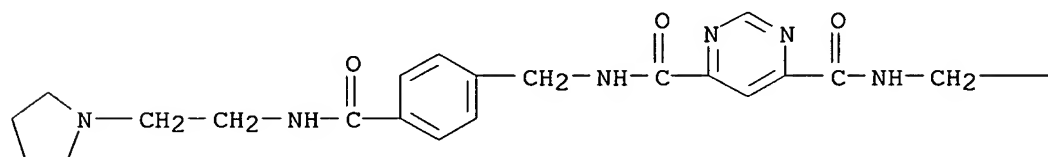
CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[(4-methyl-1-piperazinyl)carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



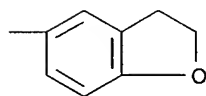
RN 691002-71-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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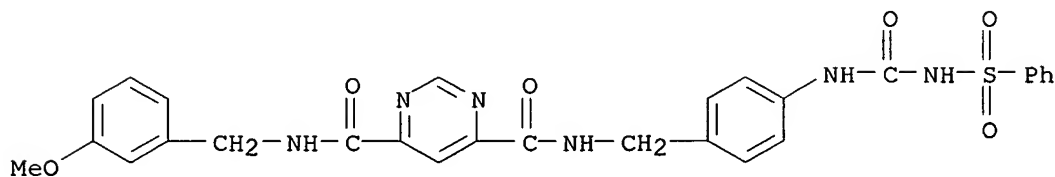


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RN 691002-72-9 CAPLUS

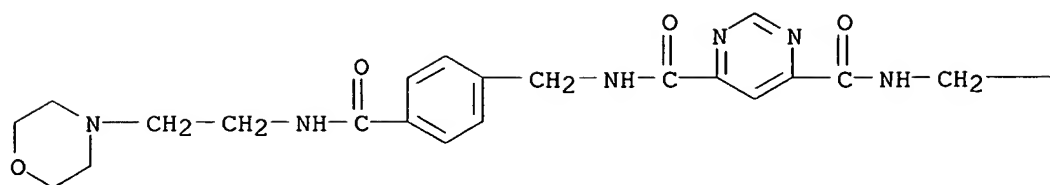
CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



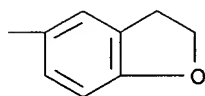
RN 691002-73-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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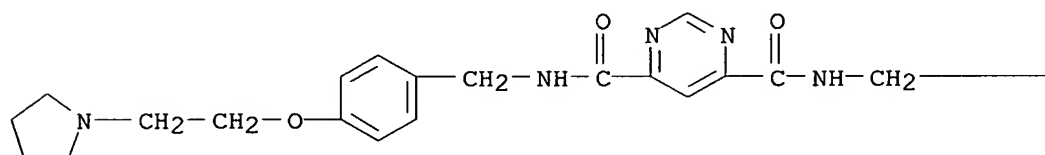
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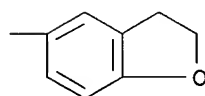
RN 691002-74-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

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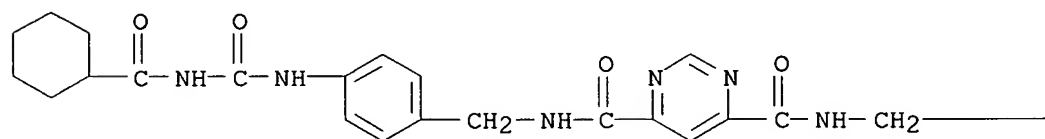
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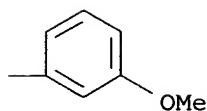
RN 691002-75-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[(cyclohexylcarbonyl)amino]carbonyl]amino]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

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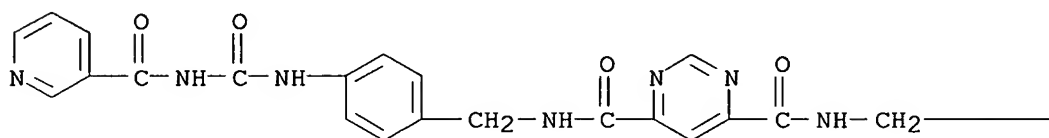
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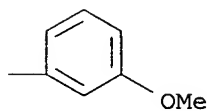
RN 691002-76-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[(3-pyridinylcarbonyl)amino]carbonyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)

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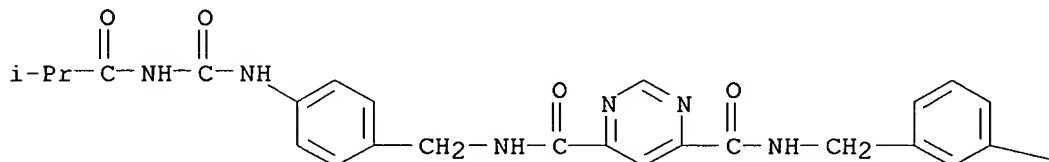
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RN 691002-77-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[(2-methyl-1-oxopropyl)amino]carbonyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)

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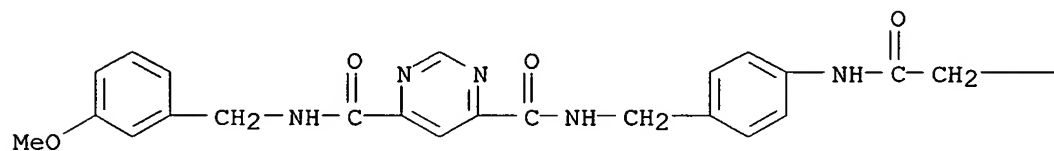
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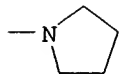
RN 691002-78-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(1-pyrrolidinylacetyl)amino]phenyl)methyl]- (9CI) (CA INDEX NAME)

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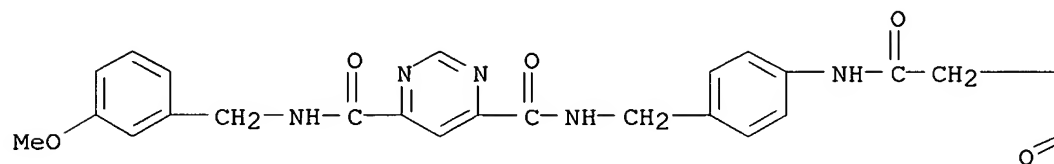
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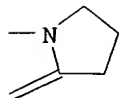
RN 691002-80-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(2-oxo-1-pyrrolidinyl)acetyl]amino]phenyl)methyl]- (9CI) (CA INDEX NAME)

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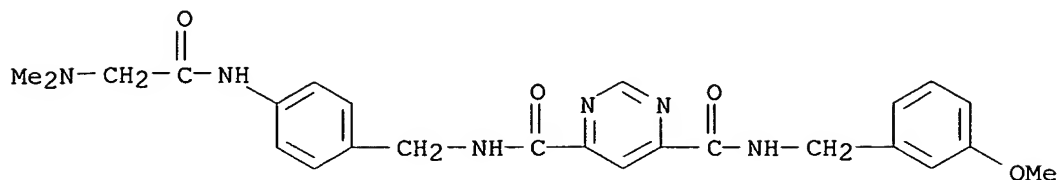
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RN 691002-84-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(dimethylamino)acetyl]amino]phenyl]me

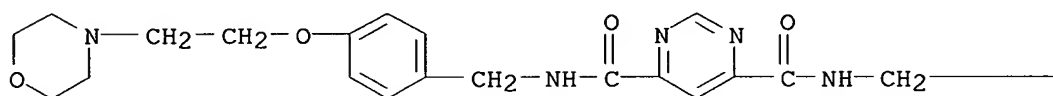
thyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



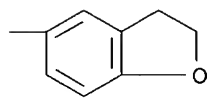
RN 691002-85-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[2-(4-morpholinyl)ethoxy]phenyl)methyl]- (9CI) (CA INDEX NAME)

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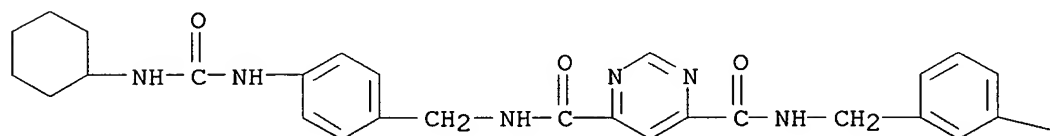
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RN 691002-86-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[(cyclohexylamino)carbonyl]amino]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

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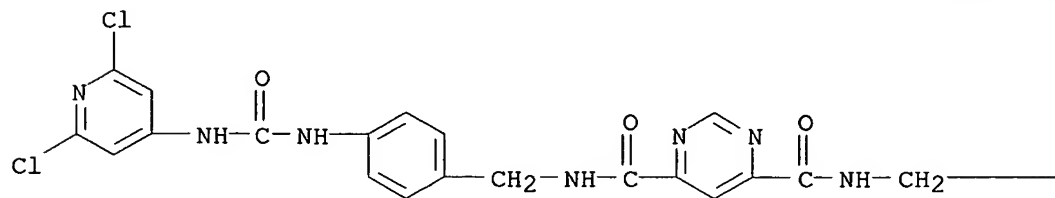
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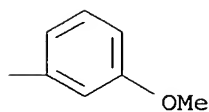
RN 691002-87-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[(2,6-dichloro-4-pyridinyl)amino]carbonyl]amino]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]-(9CI) (CA INDEX NAME)

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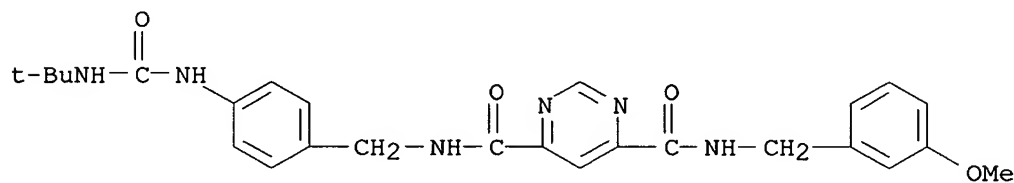


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RN 691002-88-7 CAPLUS

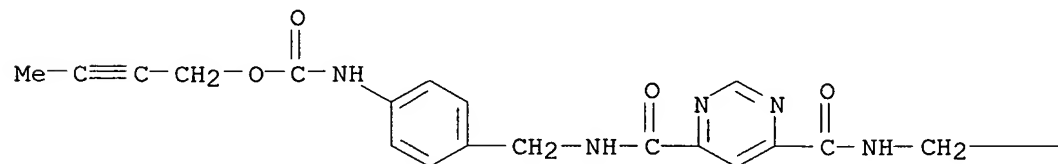
CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[(1,1-dimethylethyl)amino]carbonyl]amino]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]-(9CI) (CA INDEX NAME)

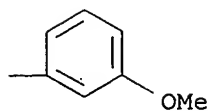


RN 691002-89-8 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-butynyl ester (9CI) (CA INDEX NAME)

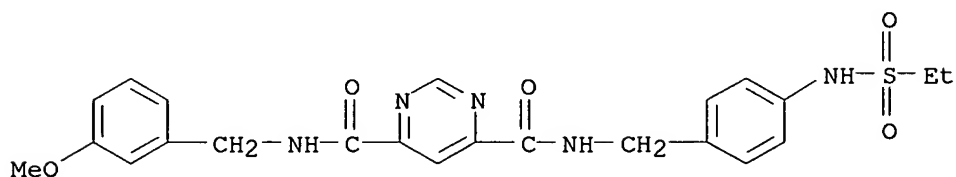
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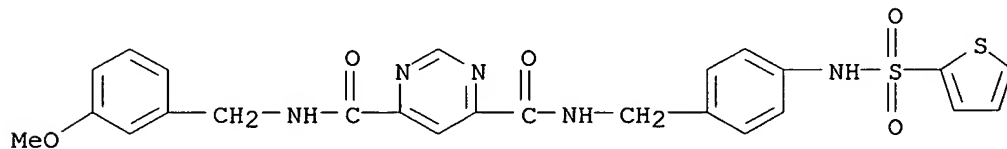
RN 691002-90-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(ethylsulfonyl)amino]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



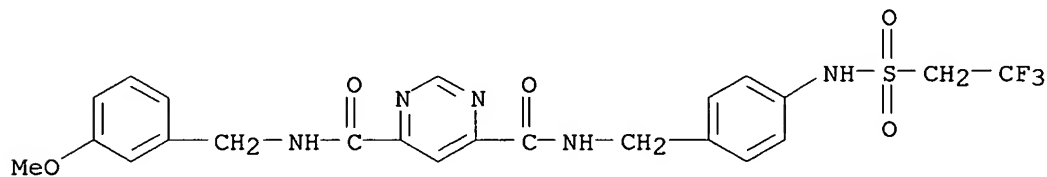
RN 691002-91-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(2-thienylsulfonyl)amino]phenyl]methyl]- (9CI) (CA INDEX NAME)



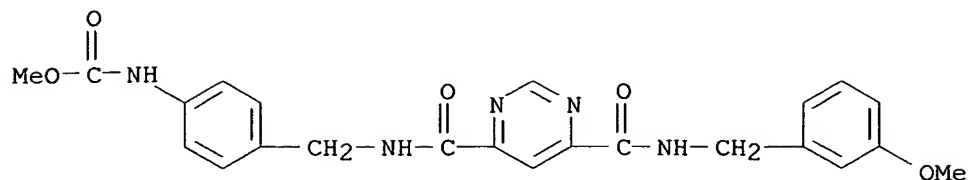
RN 691002-92-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[(2,2,2-trifluoroethyl)sulfonyl]amino]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691002-93-4 CAPLUS

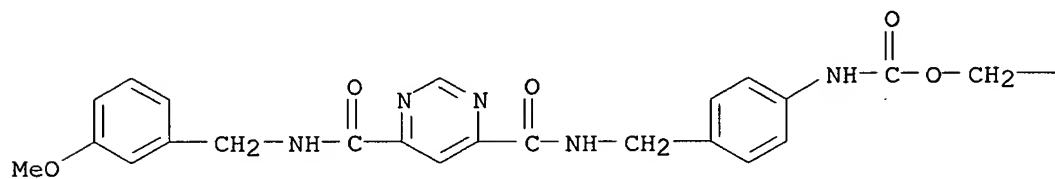
CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 691002-94-5 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-propynyl ester (9CI) (CA INDEX NAME)

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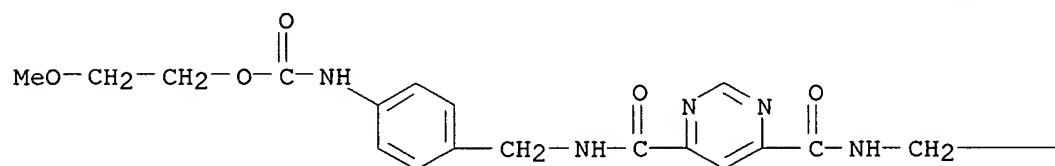
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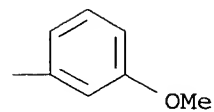
RN 691002-95-6 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-methoxyethyl ester (9CI) (CA INDEX NAME)

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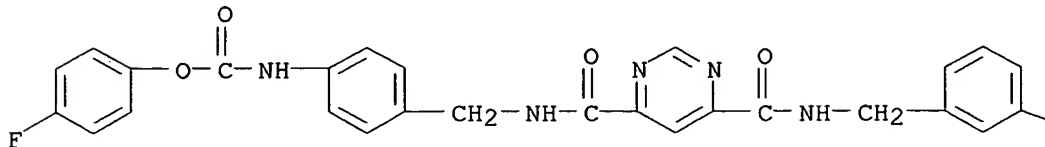


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RN 691002-96-7 CAPLUS  
 CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 4-fluorophenyl ester (9CI)  
 (CA INDEX NAME)

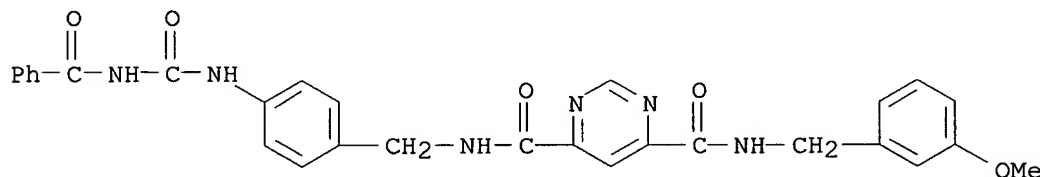
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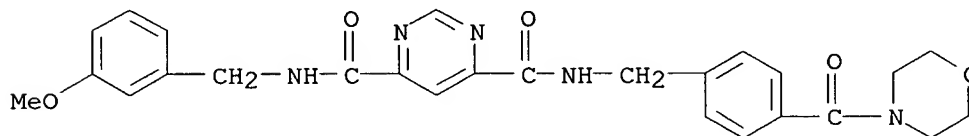
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RN 691002-97-8 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N-[[4-[(benzoylamino)carbonyl]amino]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

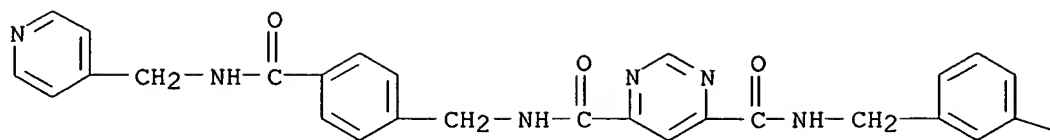


RN 691002-98-9 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-(4-morpholinylcarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691002-99-0 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(4-pyridinylmethyl)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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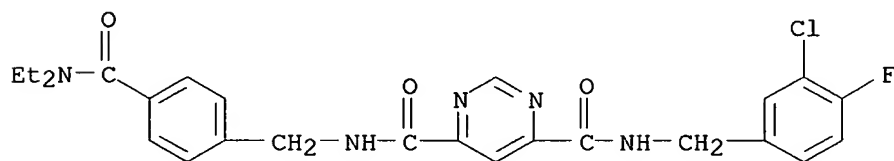


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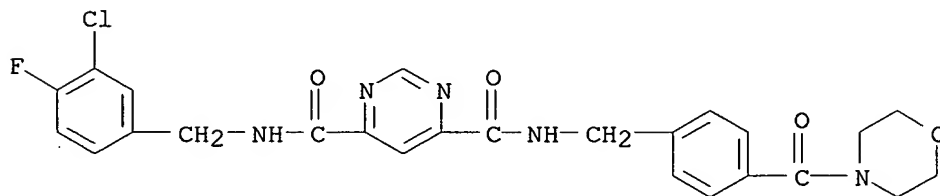
RN 691003-00-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[(diethylamino)carbonyl]phenyl)methyl]- (9CI) (CA INDEX NAME)



RN 691003-01-7 CAPLUS

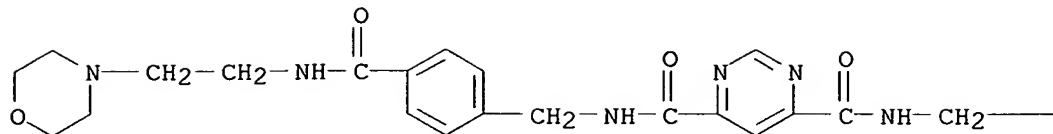
CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-(4-morpholinylcarbonyl)phenyl)methyl]- (9CI) (CA INDEX NAME)



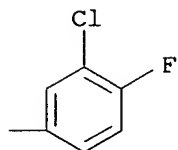
RN 691003-02-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl)methyl]- (9CI) (CA INDEX NAME)

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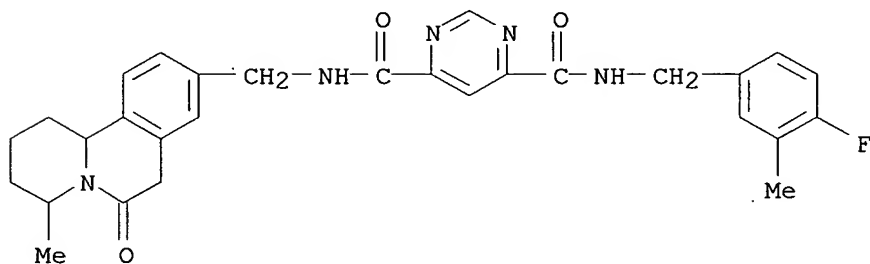


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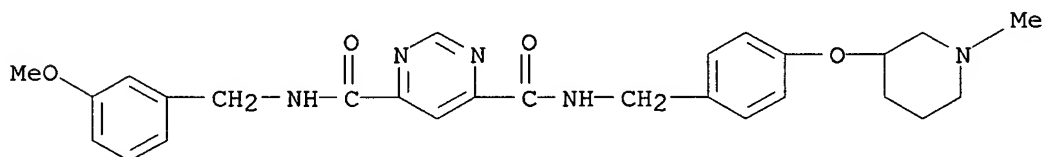
RN 691003-03-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[(1,3,4,6,7,11b-hexahydro-4-methyl-6-oxo-2H-benzo[a]quinolizin-9-yl)methyl]- (9CI) (CA INDEX NAME)



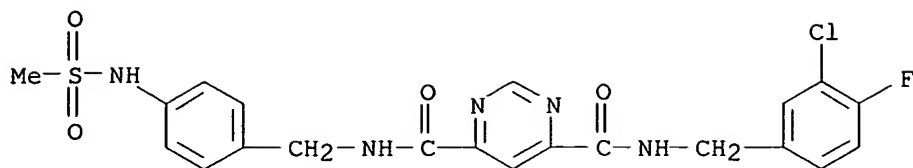
RN 691003-04-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[(1-methyl-3-piperidinyl)oxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



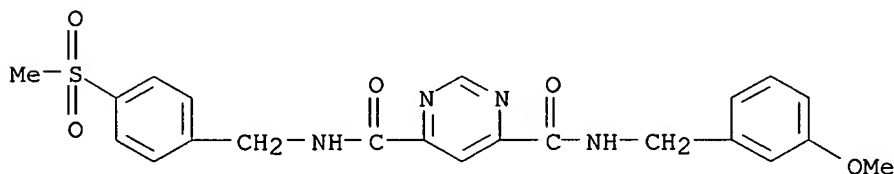
RN 691003-06-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[(methylsulfonyl)amino]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 691003-07-3 CAPLUS

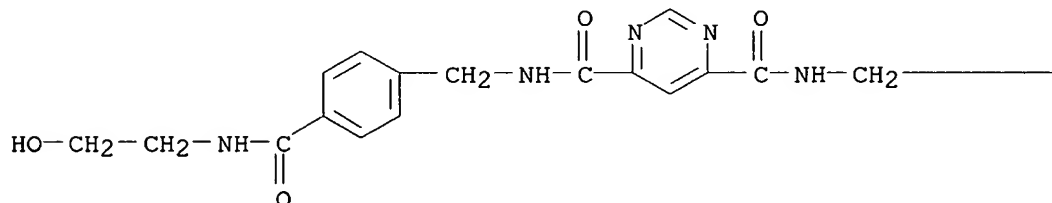
CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-(methylsulfonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



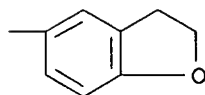
RN 691003-08-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-5-benzofuranyl)methyl]-N'-[[4-[(2-hydroxyethyl)amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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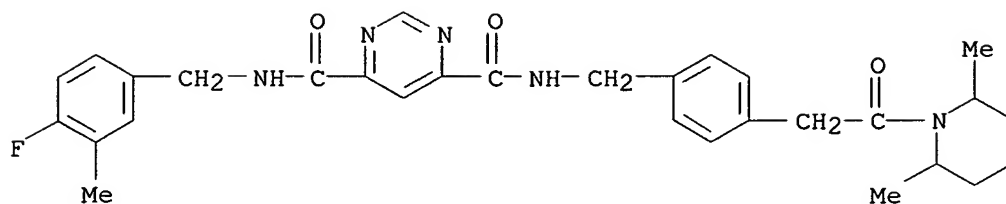


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RN 691003-09-5 CAPLUS

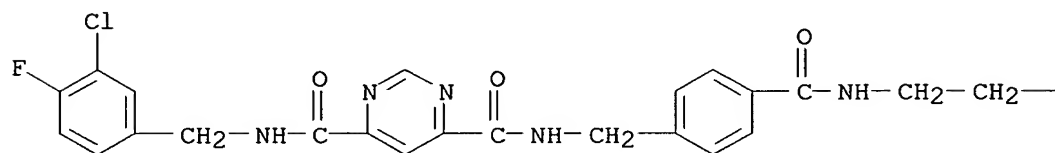
CN 4,6-Pyrimidinedicarboxamide, N-[[4-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]phenyl]methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



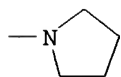
RN 691003-10-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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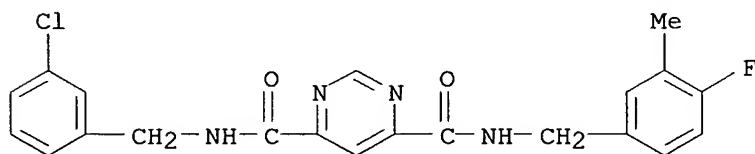


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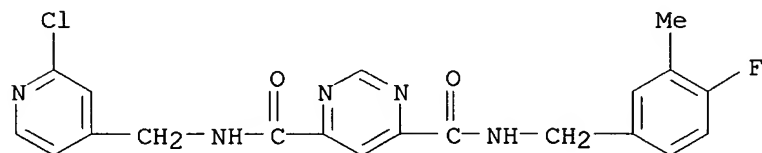
RN 691003-17-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chlorophenyl)methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



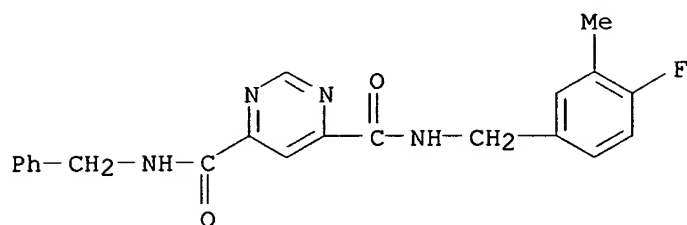
RN 691003-18-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2-chloro-4-pyridinyl)methyl]-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



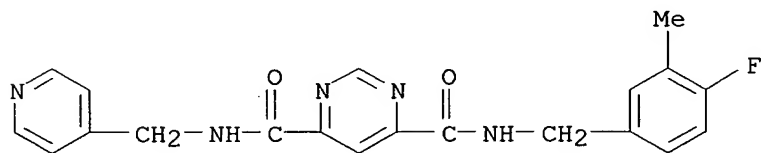
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CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)



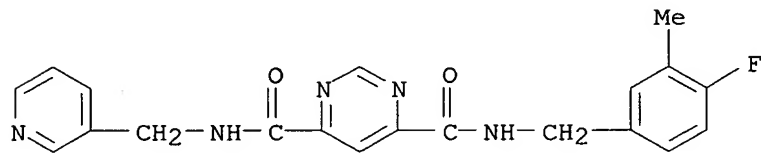
RN 691003-20-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-(4-pyridinylmethyl)- (9CI) (CA INDEX NAME)



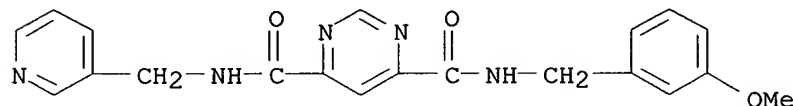
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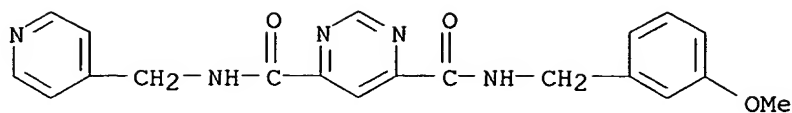
RN 691003-22-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



RN 691003-23-3 CAPLUS

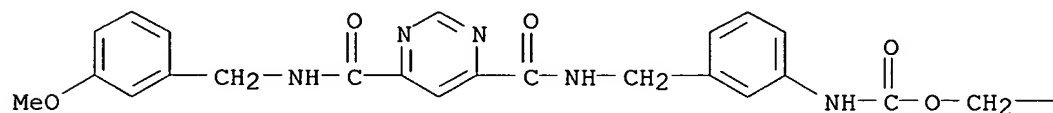
CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-(4-pyridinylmethyl)- (9CI) (CA INDEX NAME)



RN 691003-40-4 CAPLUS

CN Carbamic acid, [3-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-butynyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



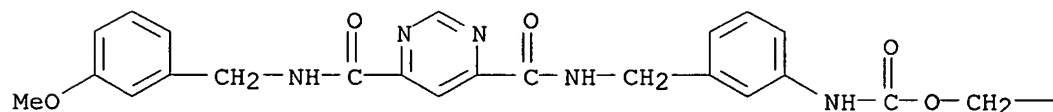
PAGE 1-B

—C≡C—Me

RN 691003-41-5 CAPLUS

CN Carbamic acid, [3-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-propynyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

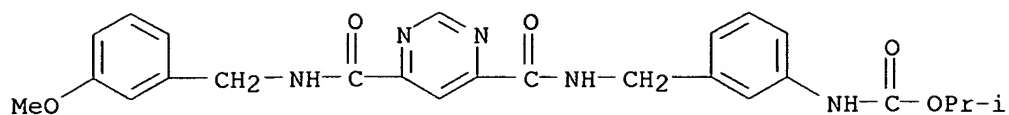


PAGE 1-B

—C≡CH

RN 691003-42-6 CAPLUS

CN Carbamic acid, [3-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



IT **690998-33-5P**

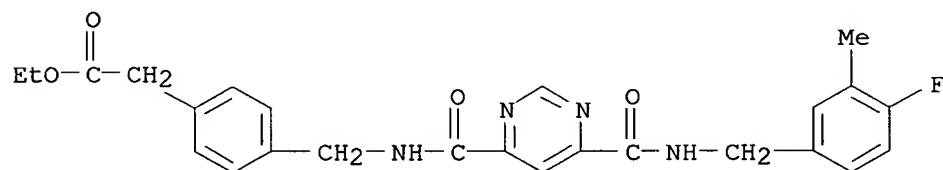
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation, saponification and inhibition of collagenases by; preparation of novel

pyrimidine-4,6-dicarboxamides for the selective inhibition of collagenases)

RN 690998-33-5 CAPLUS

CN Benzeneacetic acid, 4-[[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:408216 CAPLUS  
 DN 140:423686  
 TI Preparation of pyrimidine-4,6-dicarboxamides as inhibitors of matrix metalloproteinase-13  
 IN Klingler, Otmar; Kirsch, Reinhard; Habermann, Joerg; Weithmann, Klaus-Ulrich; Engel, Christian; Pirard, Bernard  
 PA Aventis Pharma Deutschland G.m.b.H., Germany  
 SO Ger. Offen., 25 pp.  
 CODEN: GWXXBX  
 DT Patent  
 LA German  
 FAN.CNT 2

*Same Qw.*  
~~Same Qw.~~

*No 102 (e)*

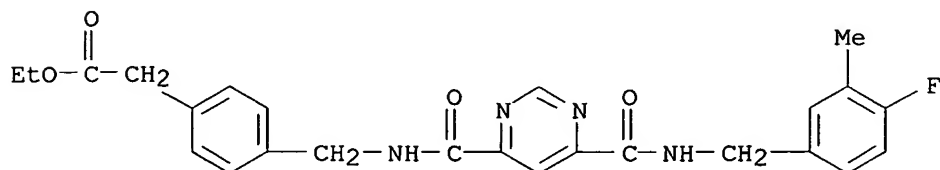
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PI	DE 10251019	A1	20040519	DE 2002-10251019	20021102	
	CA 2504153	AA	20040521	CA 2003-2504153	20031018	
	WO 2004041788	A1	20040521	WO 2003-EP11515	20031018	
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	US 2004167120	A1	20040826	US 2003-700273	20031103	
	NO 2005002628	A	20050708	NO 2005-2628	20050531	
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	US 2003-456395P	P	20030321			
	US 2003-458316P	P	20030328			
	WO 2003-EP11515	W	20031018			

*← ODP*

OS MARPAT 140:423686  
 AB Title compds. [I; R1 = H, C1-6 alkyl; R2 = (substituted) C1-6 alkyl; R3-R7 = H, halo, (substituted) C1-6 alkyl, O-C1-6-alkyl, S-C1-6-alkyl; or R4R5R6 = 5-6 membered aromatic saturated (substituted) (hetero)cyclyl], were prepared Thus, 4-[6-(3-methoxybenzylcarbonyl)pyrimidine-4-carbonylaminomethyl]benzoic acid (preparation given) in DMF was treated under stirring successively with Et2NH, O-[(cyanoethoxycarbonylmethylene)amino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU), and Et3N followed by stirring for 1 h at 0° and 12 h at room temperature to give 57% N-[4-(diethylaminocarbonyl)benzyl]-N'-(3-methoxybenzyl)pyrimidine-4,6-dicarboxamide. The latter inhibited MMP-13 with IC50 <20 nM. I can be especially used for the treatment of degenerative joint diseases.

IT **690998-33-5P**  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation of pyrimidine-4,6-dicarboxamides as inhibitors of matrix metalloproteinase-13)  
 RN 690998-33-5 CAPLUS

CN Benzeneacetic acid, 4-[[[6-[[[(4-fluoro-3-methylphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



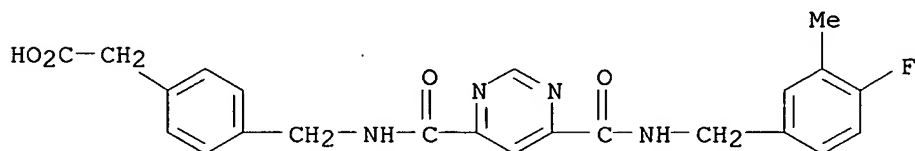
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 690998-73-3P 690998-74-4P 690998-75-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrimidine-4,6-dicarboxamides as inhibitors of matrix metalloproteinase-13)

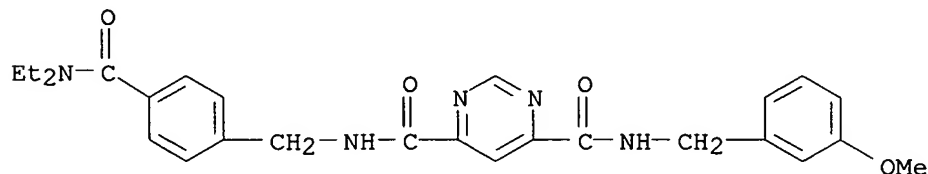
RN 690998-36-8 CAPLUS

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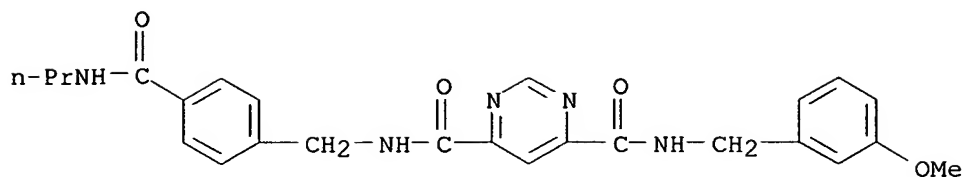
RN 690998-37-9 CAPLUS

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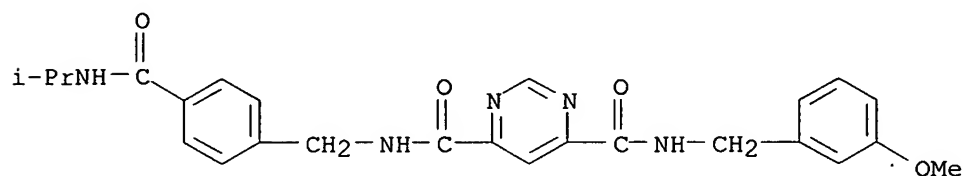
RN 690998-40-4 CAPLUS

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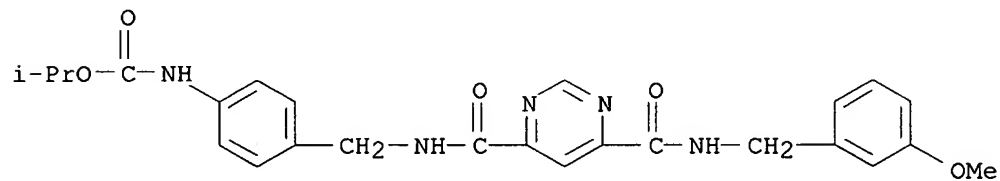
RN 690998-41-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[1-methylethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



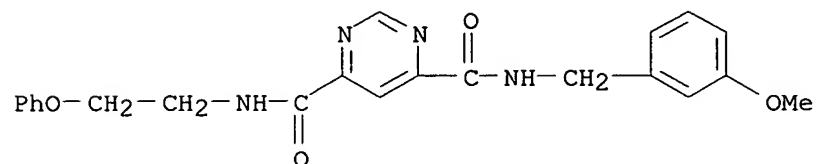
RN 690998-42-6 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



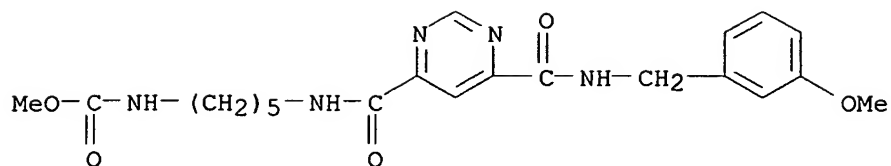
RN 690998-43-7 CAPLUS

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RN 690998-44-8 CAPLUS

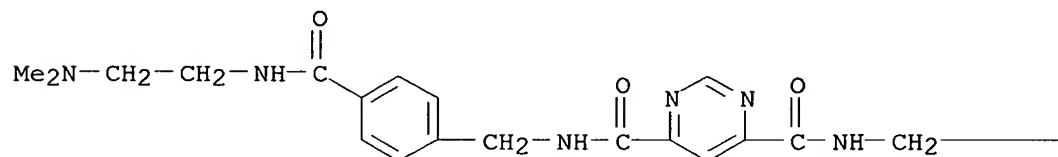
CN Carbamic acid, [5-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]pentyl]-, methyl ester (9CI) (CA INDEX NAME)



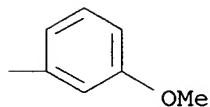
RN 690998-45-9 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[[4-[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]methyl]-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

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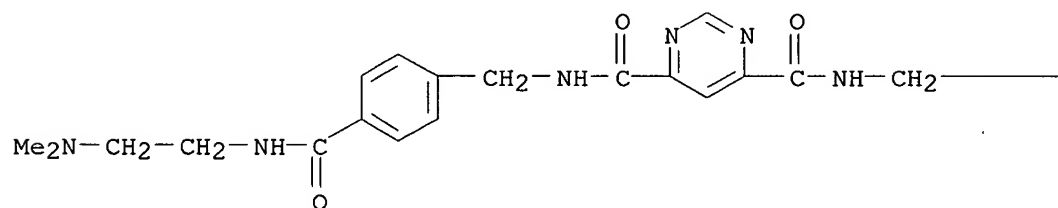
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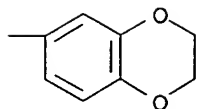
RN 690998-46-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(2,3-dihydro-1,4-benzodioxin-6-yl)methyl]-N'-[[4-[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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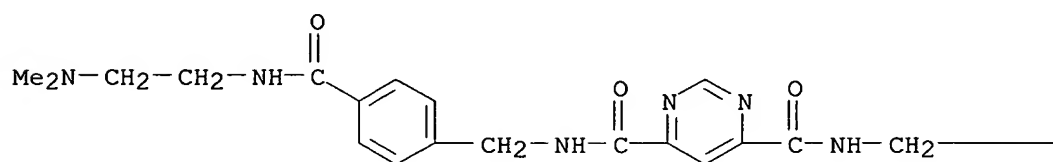
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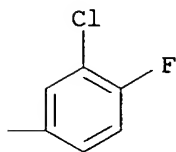
RN 690998-47-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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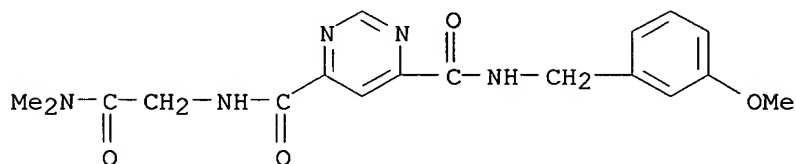


PAGE 1-B



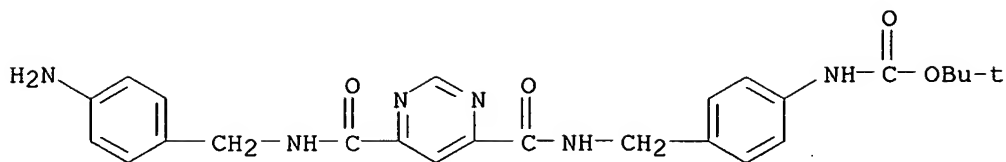
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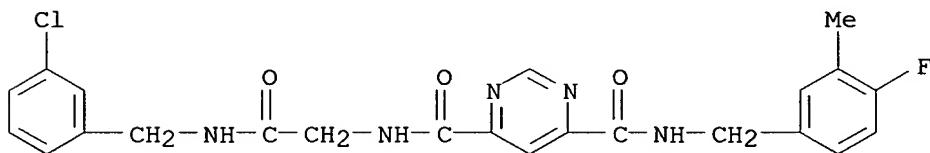
RN 690998-49-3 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(4-aminophenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



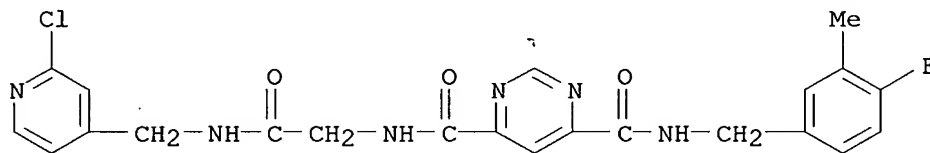
RN 690998-50-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[2-[(3-chlorophenyl)methyl]amino]-2-oxoethyl-N'-[(4-fluoro-3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



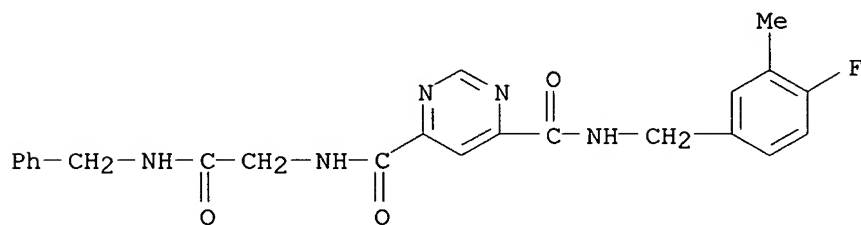
RN 690998-52-8 CAPLUS

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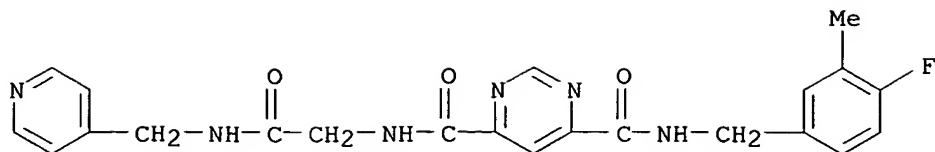
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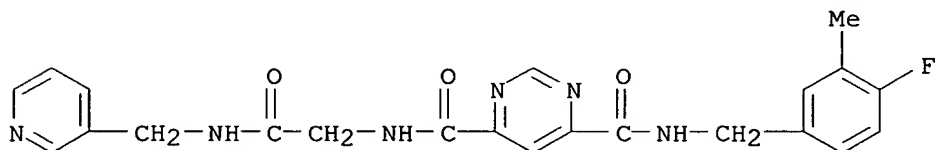
RN 690998-54-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[2-oxo-2-[(4-pyridinylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



RN 690998-55-1 CAPLUS

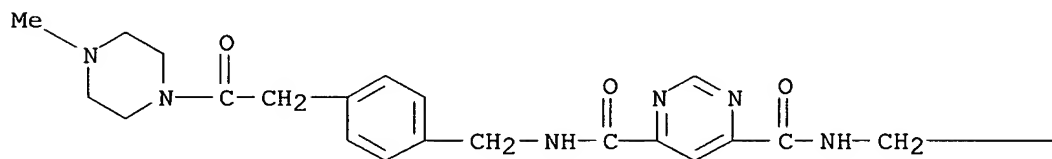
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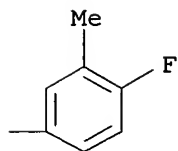
RN 690998-56-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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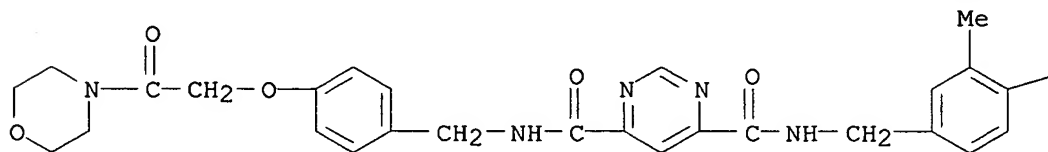
PAGE 1-B



RN 690998-57-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-(4-morpholinyl)-2-oxoethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

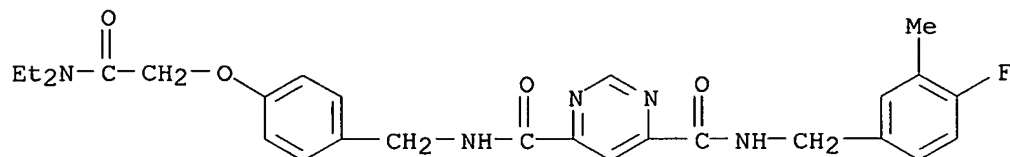
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— F

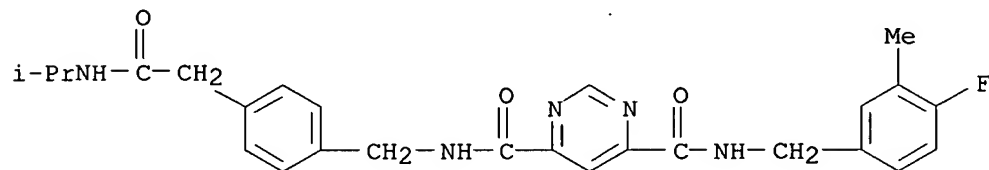
RN 690998-58-4 CAPLUS

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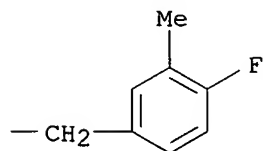
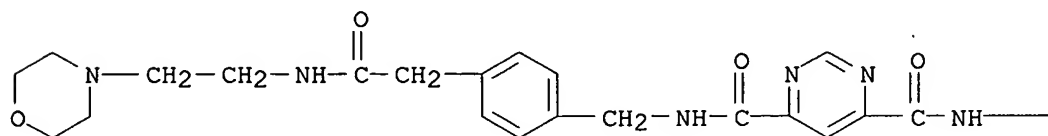
RN 690998-59-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-[(1-methylethyl)amino]-2-oxoethyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



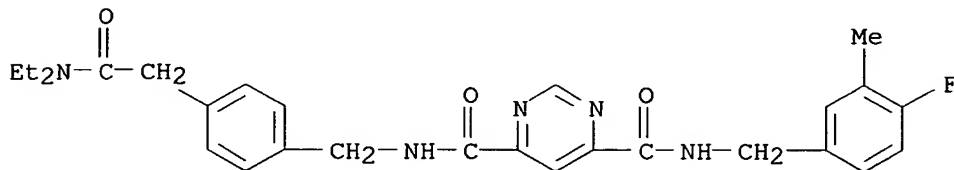
RN 690998-60-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(4-fluoro-3-methylphenyl)methyl]-N'-[[4-[2-[2-(4-morpholinyl)ethyl]amino]-2-oxoethyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



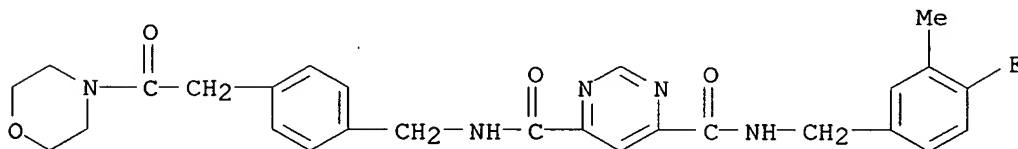
RN 690998-61-9 CAPLUS

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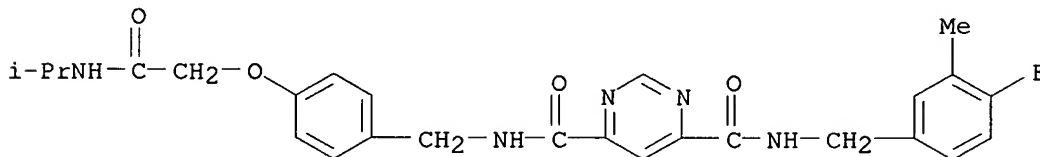
RN 690998-63-1 CAPLUS

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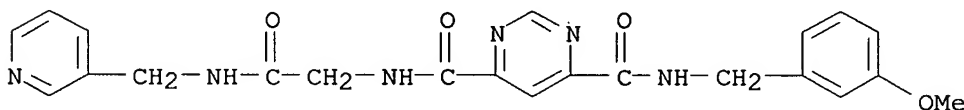
RN 690998-64-2 CAPLUS

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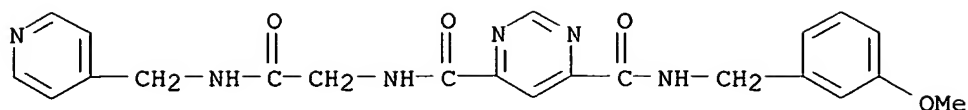
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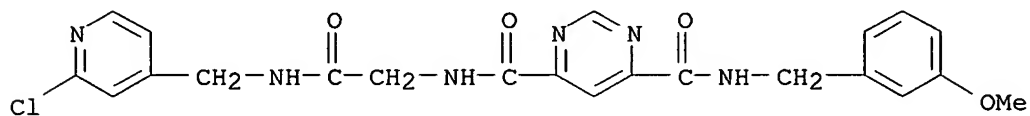
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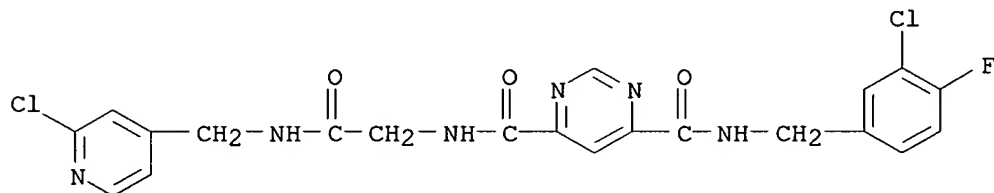
RN 690998-67-5 CAPLUS

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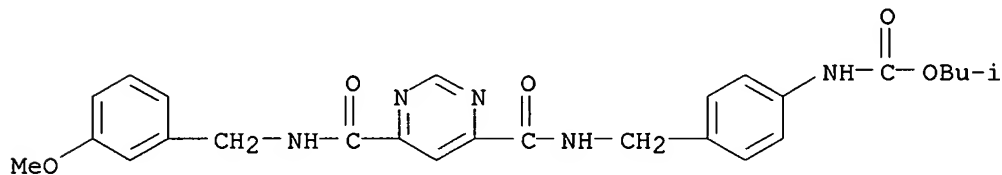
RN 690998-68-6 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[2-[(2-chloro-4-pyridinyl)methyl]amino]-2-oxoethyl]- (9CI) (CA INDEX NAME)



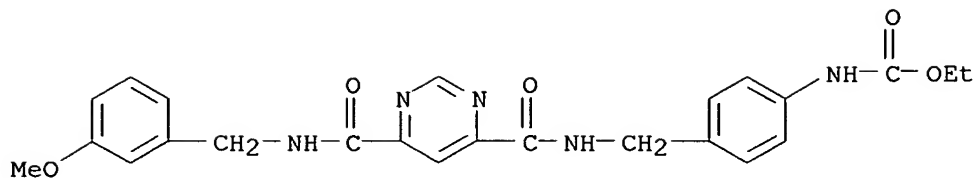
RN 690998-69-7 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-methylpropyl ester (9CI) (CA INDEX NAME)



RN 690998-70-0 CAPLUS

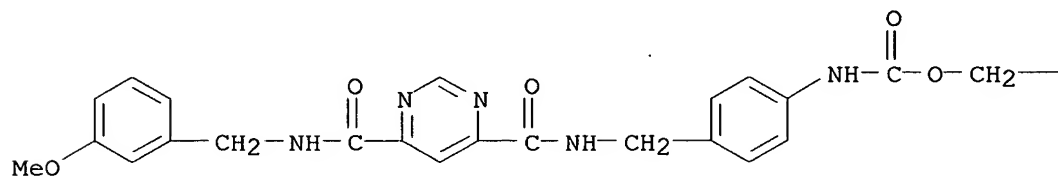
CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 690998-71-1 CAPLUS

CN Carbamic acid, [4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]phenyl]-, 2-propenyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

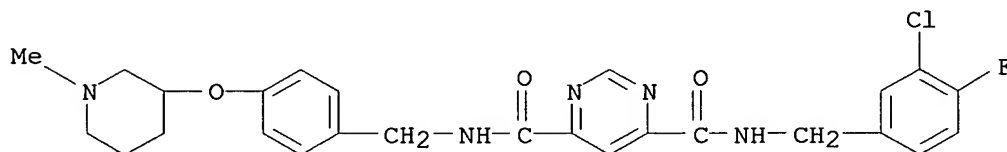


PAGE 1-B

—CH=CH<sub>2</sub>

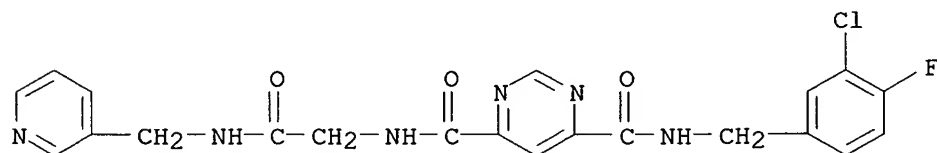
RN 690998-72-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[[4-[(1-methyl-3-piperidinyl)oxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 690998-73-3 CAPLUS

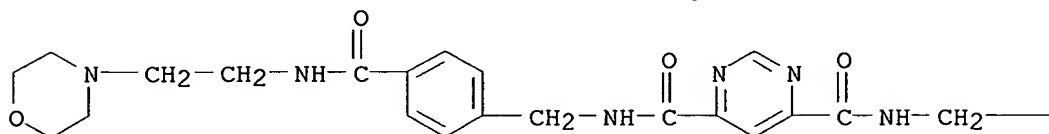
CN 4,6-Pyrimidinedicarboxamide, N-[(3-chloro-4-fluorophenyl)methyl]-N'-[2-oxo-2-[(3-pyridinylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)



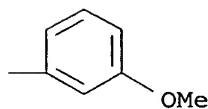
RN 690998-74-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



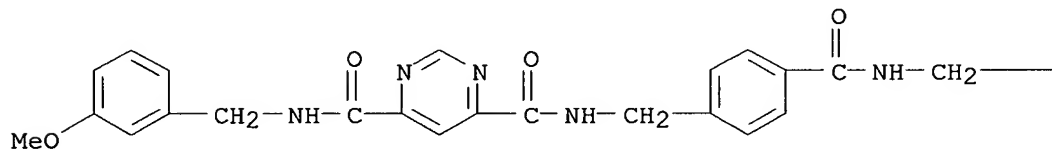
PAGE 1-B



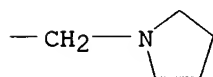
RN 690998-75-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methoxyphenyl)methyl]-N'-[[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



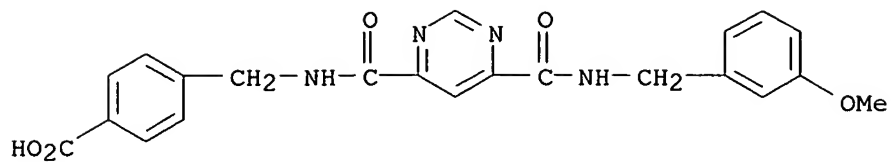
IT 448949-22-2P 448949-23-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrimidine-4,6-dicarboxamides as inhibitors of matrix metalloproteinase-13)

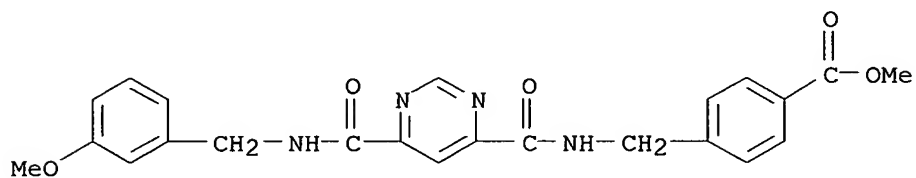
RN 448949-22-2 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



RN 448949-23-3 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:467290 CAPLUS  
 DN 139:53028  
 TI Preparation of 2,4-pyridinedicarboxamides and 4,6-pyrimidinedicarboxamides as inhibitors of collagenase (MMP 13)  
 IN Habermann, Joerg; Weithmann, Klaus-Ulrich; Kogler, Herbert; Kirsch, Reinhard; Wehner, Volkmar  
 PA Aventis Pharma Deutschland G.m.b.H., Germany  
 SO Ger. Offen., 20 pp.  
 CODEN: GWXXBX  
 DT Patent  
 LA German  
 FAN.CNT 1

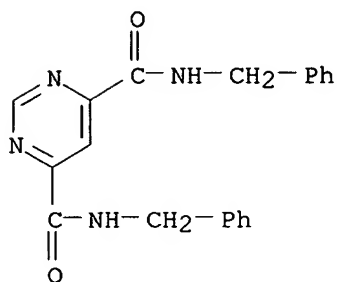
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10160357	A1	20030618	DE 2001-10160357	20011208
	CA 2469625	AA	20030619	CA 2002-2469625	20021125
	WO 2003049738	A1	20030619	WO 2002-EP13240	20021125
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	US 2003229103	A1	20031211	US 2002-65994	20021209
	US 6933298	B2	20050823		
PRAI	DE 2001-10160357	A	20011208		
	US 2002-358887P	P	20020222		
	WO 2002-EP13240	W	20021125		
OS	MARPAT 139:53028				
AB	Title compds. [I; A = CH, N; R1-R3 = H, halo, (halogenated) alkyl, alkoxy, OH, CO2R4, cyano, NR5R6, etc.; R4 = H, alkyl; R5, R6 = H, alkyl, alkylcarbonyl, etc.; or R1R2, R2R3 = 5-6 membered (aromatic) (saturated) (hetero)cyclyl], were prepd for the treatment of degenerative joint diseases. Thus, 4,6-pyrimidinedicarboxylic acid in SOCl2 was stirred for 2 h at 85° followed by addition of CH2Cl2 at room temperature and Et3N at 0°. The reaction mixture was further stirred with 3-chloro-4-fluorobenzylamine for 15 min to give 40% N,N-bis(3-chloro-4-fluorobenzyl)pyrimidine-4,6-dicarboxamide. The latter inhibited collagenase 3 (MMP 13) with IC50 = 23 nM.				
IT	135002-40-3P 448949-33-5P 448949-35-7P 448949-36-8P 544678-67-3P 544678-69-5P 544678-70-8P 544678-75-3P 544678-76-4P 544678-78-6P 544678-79-7P 544678-80-0P 544678-81-1P 544678-82-2P 544678-83-3P 544678-85-5P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of pyridine- and pyrimidinedicarboxamides as inhibitors of				

No

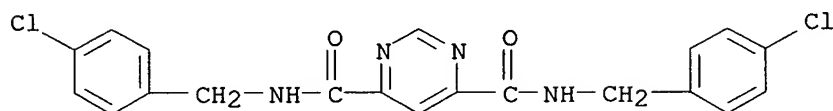
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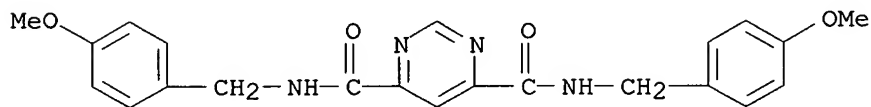
collagenase (MMP 13))  
 RN 135002-40-3 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N,N'-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



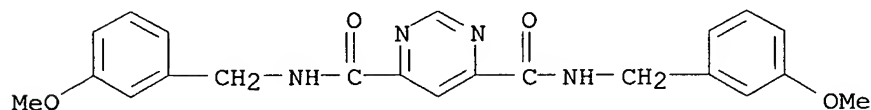
RN 448949-33-5 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(4-chlorophenyl)methyl]- (9CI) (CA INDEX NAME)



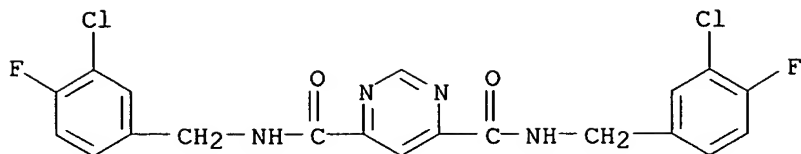
RN 448949-35-7 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(4-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 448949-36-8 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

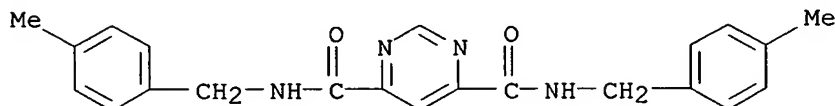


RN 544678-67-3 CAPLUS  
 CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3-chloro-4-fluorophenyl)methyl]- (9CI) (CA INDEX NAME)



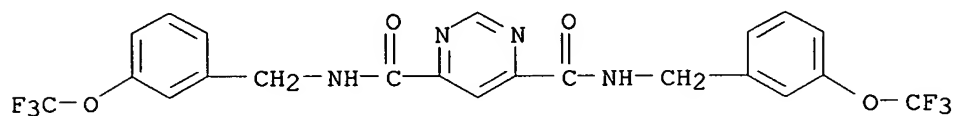
RN 544678-69-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(4-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



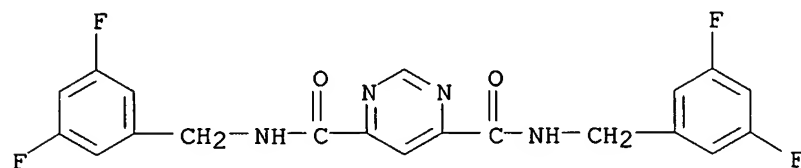
RN 544678-70-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[[3-(trifluoromethoxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



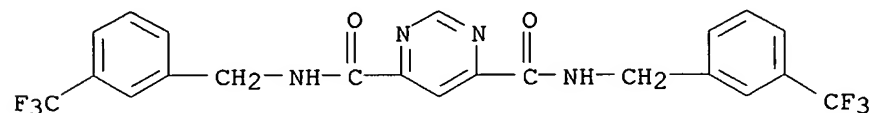
RN 544678-75-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3,5-difluorophenyl)methyl]- (9CI) (CA INDEX NAME)



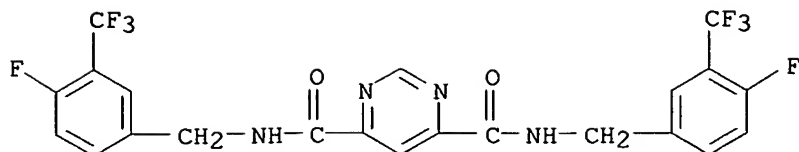
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CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[[3-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



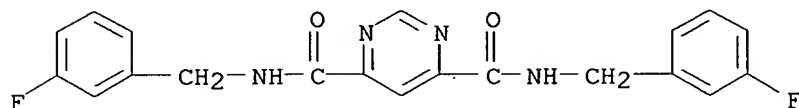
RN 544678-78-6 CAPLUS

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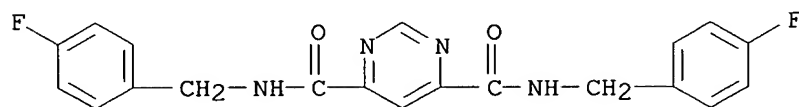
RN 544678-79-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3-fluorophenyl)methyl]- (9CI) (CA INDEX NAME)



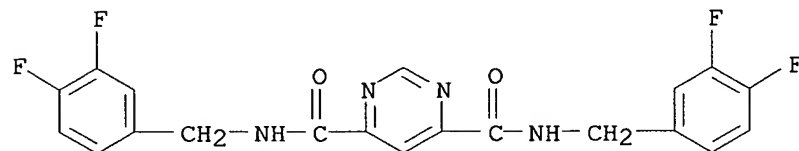
RN 544678-80-0 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(4-fluorophenyl)methyl]- (9CI) (CA INDEX NAME)



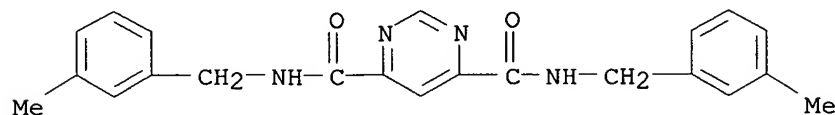
RN 544678-81-1 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3,4-difluorophenyl)methyl]- (9CI) (CA INDEX NAME)



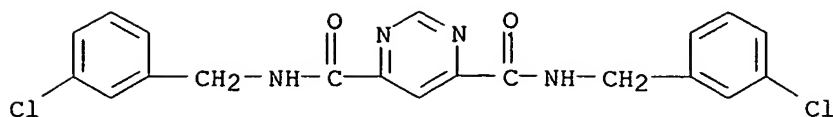
RN 544678-82-2 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



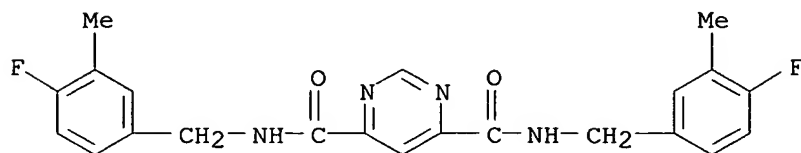
RN 544678-83-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3-chlorophenyl)methyl]- (9CI) (CA INDEX NAME)



RN 544678-85-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(4-fluoro-3-methylphenyl)methyl]-  
(9CI) (CA INDEX NAME)



IT 544678-87-7P 544678-88-8P 544678-89-9P

544678-90-2P 544678-91-3P 544678-92-4P

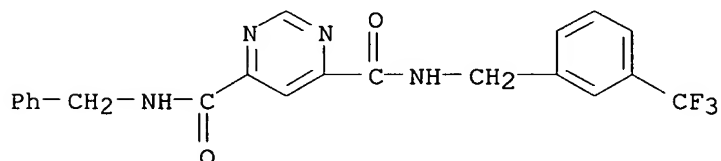
544678-93-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation of pyridine- and pyrimidinedicarboxamides as inhibitors of  
collagenase (MMP 13))

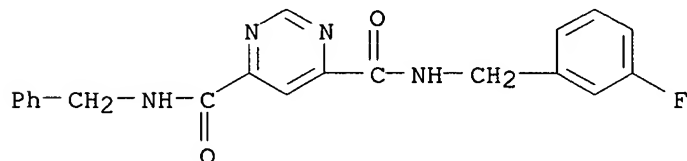
RN 544678-87-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-(phenylmethyl)-N'-[[3-  
(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 544678-88-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-fluorophenyl)methyl]-N'-(phenylmethyl)-  
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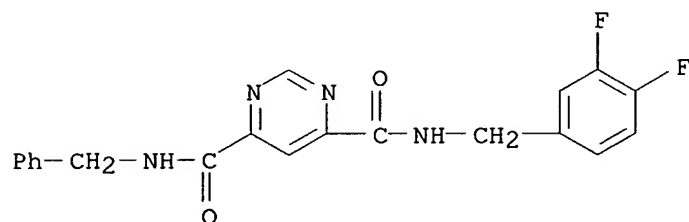
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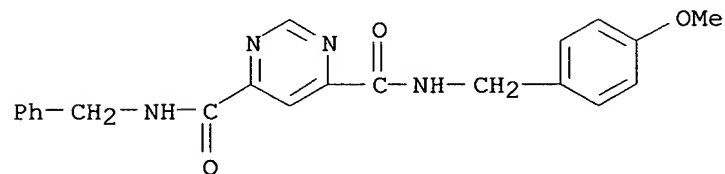
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CN 4,6-Pyrimidinedicarboxamide, N-[(3,4-difluorophenyl)methyl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)



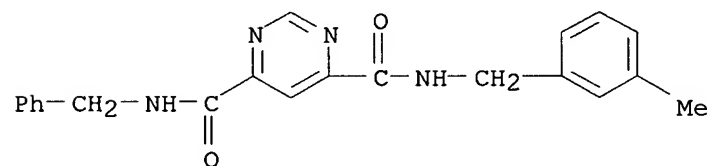
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CN 4,6-Pyrimidinedicarboxamide, N-[(4-methoxyphenyl)methyl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)



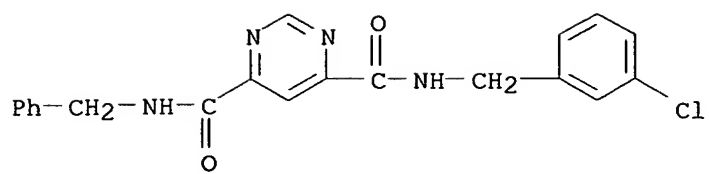
RN 544678-92-4 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-methylphenyl)methyl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 544678-93-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-[(3-chlorophenyl)methyl]-N'-(phenylmethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:637659 CAPLUS

DN 137:185500

TI Preparation and formulation of pyrimidine-4,6-dicarboxamides as MMP-13 inhibitors

IN Barvian, Nicole Chantel; Patt, William Chester

PA Warner-Lambert Company, USA

SO PCT Int. Appl., 42 pp.

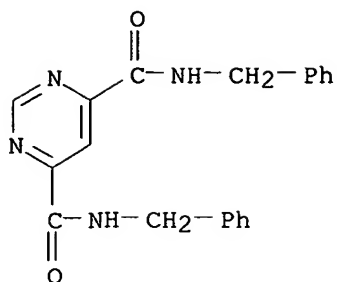
CODEN: PIXXD2

DT Patent

LA English

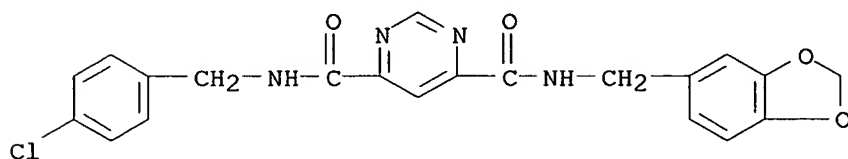
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	US 6936616	B2	20050830		
PRAI	US 2001-268779P	P	20010214		
	WO 2002-IB190	W	20020118		
OS	MARPAT 137:185500				
AB	Z[C(:X)R]2 [each R independently = OR4 or NR4R5; R4,R5 = H, alkyl, (hetero)aryl, etc.; NR4R5 = heterocyclyl; X = O or S; Z = 2-(un)substituted pyrimidine-4,6-diyl] were prepared as MMP-13 inhibitors (no data). Thus, pyrimidine-4,6-dicarboxylic acid was amidated by PhCH2NH2 to give pyrimidine-4,6-dicarboxylic acid bis(benzylamide).				
IT	135002-40-3P 448949-19-7P 448949-20-0P 448949-21-1P 448949-22-2P 448949-23-3P 448949-24-4P 448949-25-5P 448949-30-2P 448949-31-3P 448949-33-5P 448949-35-7P 448949-36-8P 448949-37-9P 448949-38-0P				
	RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)				
	(preparation and formulation of pyrimidine-4,6-dicarboxamides as MMP-13 inhibitors)				
RN	135002-40-3 CAPLUS				
CN	4,6-Pyrimidinedicarboxamide, N,N'-bis(phenylmethyl)- (9CI) (CA INDEX NAME)				



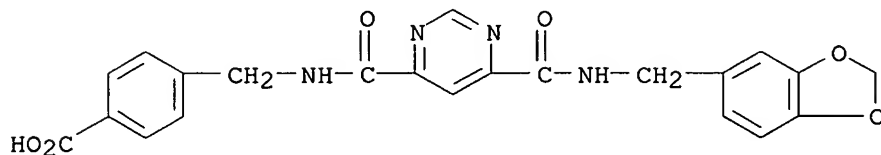
RN 448949-19-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-(1,3-benzodioxol-5-ylmethyl)-N'-[(4-chlorophenyl)methyl]- (9CI) (CA INDEX NAME)



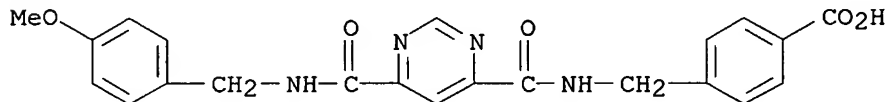
RN 448949-20-0 CAPLUS

CN Benzoic acid, 4-[[[6-[[[1,3-benzodioxol-5-ylmethyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



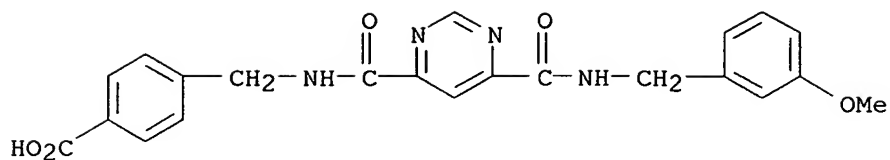
RN 448949-21-1 CAPLUS

CN Benzoic acid, 4-[[[6-[[[4-methoxyphenyl]methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



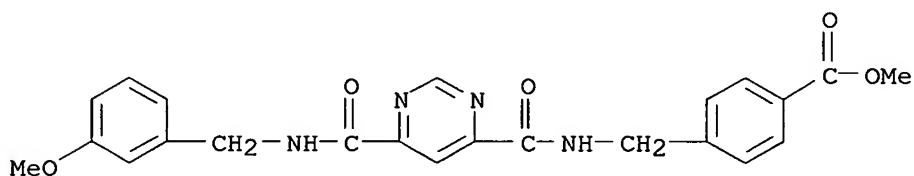
RN 448949-22-2 CAPLUS

CN Benzoic acid, 4-[[[6-[[[3-methoxyphenyl]methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



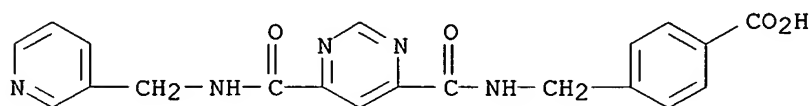
RN 448949-23-3 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(3-methoxyphenyl)methyl]amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)



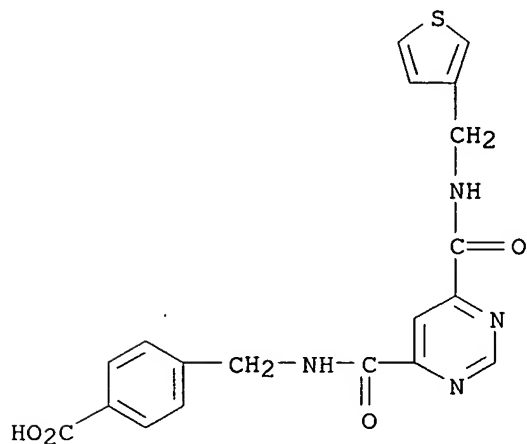
RN 448949-24-4 CAPLUS

CN Benzoic acid, 4-[[[6-[[[(3-pyridinylmethyl)amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



RN 448949-25-5 CAPLUS

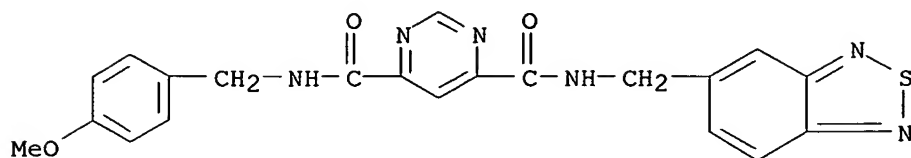
CN Benzoic acid, 4-[[[6-[[[(3-thienylmethyl)amino]carbonyl]-4-pyrimidinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



RN 448949-30-2 CAPLUS

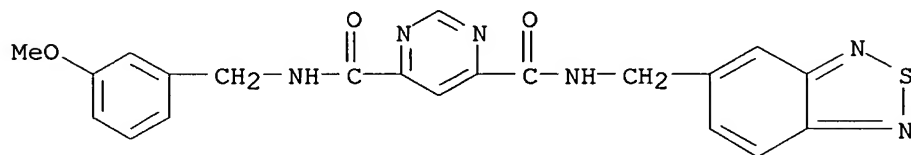
CN 4,6-Pyrimidinedicarboxamide, N-(2,1,3-benzothiadiazol-5-ylmethyl)-N'-[(4-

methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



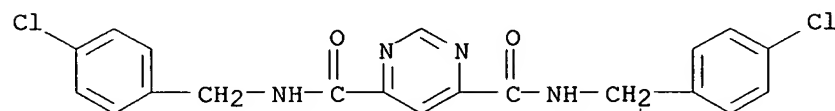
RN 448949-31-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N-(2,1,3-benzothiadiazol-5-ylmethyl)-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



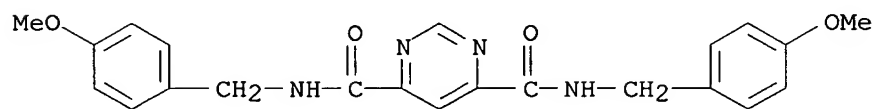
RN 448949-33-5 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(4-chlorophenyl)methyl]- (9CI) (CA INDEX NAME)



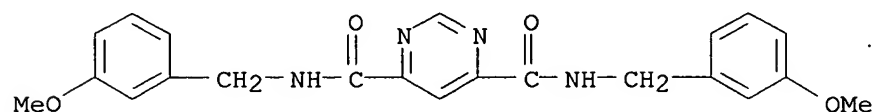
RN 448949-35-7 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(4-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



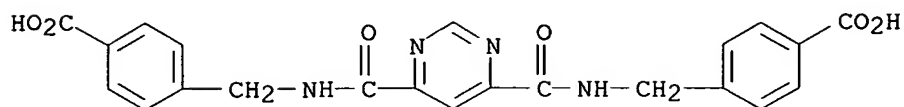
RN 448949-36-8 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



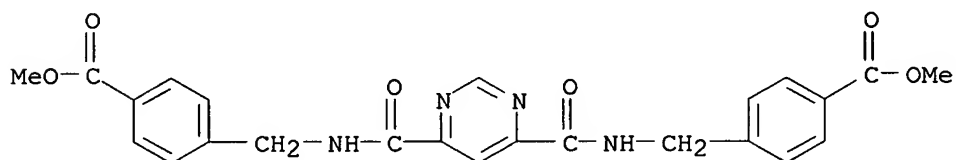
RN 448949-37-9 CAPLUS

CN Benzoic acid, 4,4'-[4,6-pyrimidinediylbis(carbonyliminomethylene)]bis-  
(9CI) (CA INDEX NAME)



RN 448949-38-0 CAPLUS

CN Benzoic acid, 4,4'-[4,6-pyrimidinediylbis(carbonyliminomethylene)]bis-,  
dimethyl ester (9CI) (CA INDEX NAME)



RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1991:471610 CAPLUS  
 DN 115:71610  
 TI Preparation of pyrimidine-4,6-dicarboxylic acid diamides as proline- and lysine hydroxylase inhibitors  
 IN Baader, Ekkehard; Bickel, Martin; Guenzler-Pukall, Volkmar; Henke, Stephan  
 PA Hoechst A.-G., Germany  
 SO Eur. Pat. Appl., 15 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA German  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 418797	A2	19910327	EP 1990-117894	19900918
	EP 418797	A3	19910508		
	EP 418797	B1	19940824		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	DE 3931432	A1	19910404	DE 1989-3931432	19890921
	ES 2062239	T3	19941216	ES 1990-117894	19900918
	DD 295835	A5	19911114	DD 1990-344102	19900919
	US 5130317	A	19920714	US 1990-584655	19900919
	SU 1836359	A3	19930823	SU 1990-4831137	19900919
	IL 95740	A1	19940731	IL 1990-95740	19900919
	CA 2025799	AA	19910322	CA 1990-2025799	19900920
	NO 9004114	A	19910322	NO 1990-4114	19900920
	AU 9062698	A1	19910411	AU 1990-62698	19900920
	AU 633142	B2	19930121		
	ZA 9007535	A	19910626	ZA 1990-7535	19900920
	JP 03240776	A2	19911028	JP 1990-249018	19900920
	PL 164989	B1	19941031	PL 1990-286972	19900920
	HU 55002	A2	19910429	HU 1990-6007	19900921
	HU 207853	B	19930628		
PRAI	DE 1989-3931432	A	19890921		

OS MARPAT 115:71610

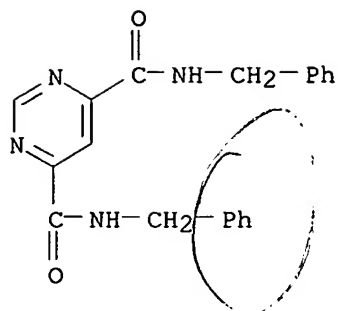
AB Title compds. [I; R1 = (substituted) alkyl, alkenyl, alkynyl, (benzo-annelated) cycloalkyl, (substituted) (hetero)aryl, amino; R2 = H, R1; R1R2N = Q1; R3 = H, (substituted) Ph, alkyl, alkenyl, alkynyl, alkoxy carbonyl, cycloalkyl; n = 1-3], were prepared Thus, pyrimidine-4,6-dicarboxylic acid was refluxed .apprx.3 h with SOCl2 and cat. DMF in PhMe; the mixture was cooled to 0-10° and treated with PhCH2NH2 and Et3N followed by 12 h stirring at room temperature to give title compound II. II at 50 mg/kg orally daily showed 21% reduction in CCl4-induced liver hydroxyproline concentration in rats.

IT **135002-40-3P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of, as proline- and lysinehydroxylase inhibitor)

RN 135002-40-3 CAPLUS

CN 4,6-Pyrimidinedicarboxamide, N,N'-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 11:55:51 ON 04 JAN 2006)

FILE 'STNGUIDE' ENTERED AT 11:56:14 ON 04 JAN 2006

FILE 'HOME' ENTERED AT 11:56:19 ON 04 JAN 2006

FILE 'REGISTRY' ENTERED AT 11:56:23 ON 04 JAN 2006

L1 STRUCTURE UPLOADED

L2 10 S L1 SSS SAM

L3 254 S L1 SSS FUL

FILE 'CAPLUS' ENTERED AT 11:58:52 ON 04 JAN 2006

L4 7 S L3

FILE 'CAOLD' ENTERED AT 11:59:32 ON 04 JAN 2006

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L5 0 L3

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COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.44

205.41

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

0.00

-5.25

STN INTERNATIONAL LOGOFF AT 11:59:42 ON 04 JAN 2006